New developments in diagnosis and treatment of deep vein thrombosis

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Hermes &merchant approach Asclepius and his daughters (Meditrine ,Hygeia and Panacea). Engraved from an original in the Museum Pio Clemens Rome.

New developments in diagnosis and Treatment of deep vein thrombosis

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MEDICINE ART OR SCIENCE?

"In early times, medicine was an art, which took its place at the side of poetry and painting; today they try to make a science of it, placing it beside mathematics, astronomy, and physics."

Armand Trousseau

Lectures on Clinical Medicine (vol 2), The New Sydenham Society, 1869.

Voor Hugo

Contents

Chapter 1

General Introduction

EVIDENCE BASED MEDICINE

Over the last ten years there has been an increased application of results of clinical research as well as translational basic research based evidence in health care practice and decision making; a concept called evidence based medicine. Due to the large scale on which research is performed, and thus evidence is generated in the field of thrombosis as well as in other areas, reviews that summarize research have become mandatory for coping with this increasing amount of evidence. Synthesized knowledge has become an essential part of modern medicine, making patient care more up to date, dynamic and less dependent on the personal experience of individual doctors. At the same time evidence based medicine may stimulate doctors to become involved in research contributing to the advance of patient care. In medical education as well as in medical practice both systematic reviews and narrative reviews have their own appropriate place. In part one of this thesis an overview is given of the requirements of systematic reviews. In part two a systematic review is described and two narrative reviews are presented in part three of this thesis.

VENOUS THROMBOEMBOLISM

Venous Thrombo Embolism (VTE) is a multi factorial disease and multiple acquired and genetic factors, commonly referred to as "risk factors", are involved in its etiology. VTE occurs in 2-3 per 1000 persons/year and is therefore considered a common disorder. [1] The clinical diagnosis is challenging due to the ambiguous clinical presentation, and can only be confirmed by the use of objective diagnostic methods in a proportion of the patients with a clinical suspicion of the disease [2-4]. Venography and pulmonary angiography are the gold standards for the diagnosis of deep vein thrombosis (DVT) and pulmonary embolism (PE) respectively, but these diagnostic methods are hardly ever used anymore because of their invasive nature.

Serial ultrasonography is a safe approach for the diagnosis of DVT in symptomatic patients [5].Similarly, CT scanning is documented to be safe in the diagnosis of PE [6] Since VTE is a potentially life threatening disorder, current

practice is therefore simply to refer all patients with signs or symptoms suspected for VTE for objective testing to specialized diagnostic services. Objective testing provides the referring primary care physician with the assurance that a thrombosis is not missed. [2,5] Although the objective tests for DVT have proved to be safe, the improved access to non-invasive testing together with a declining tolerance to diagnostic uncertainty, has over the last 20 years led to a decrease from 35% to 20% in the proportion of patients in whom the diagnosis is confirmed. [2- 6]

This renders the approach in which all patients are subjected to objective testing inefficient and costly.

DIAGNOSTIC STRATEGIES IN SECONDARY CARE

In the last two decades, there has been a tendency towards a more selective use of additional imaging tests. Patients were selected based on a high clinical score, indicating high probability for VTE. Evaluation of clinical probability scores however made evident that clinical probability alone is not sufficient to safely exclude venous thromboembolism [7]. A combination of a D-dimer assay and clinical probability as a first step in a diagnostic work-up was introduced by Wells et al [8]. D-dimer is a fibrin specific degradation product and is used as a marker for endogenous fibrinolysis in D-dimer assays. Since then, multiple studies managing patients with suspected VTE based on clinical probability in combination with a D-dimer assay result have been performed [9-19] in secondary care facilities. In this thesis a systematic review is described assessing the safety of withholding anticoagulant treatment in patients suspected of DVT based on a diagnostic work-up that combines clinical appraisal and a laboratory test result, and the efficiency in terms of reduction of ultrasound examinations.

Nevertheless, all patients still have to be referred to hospital. It would be far more convenient and efficient if selection could be done at initial presentation in general practice.

DIAGNOSTIC STRATEGIES IN PRIMARY CARE

Before the diagnostic work-up (based on a clinical decision rule and a laboratory D-dimer test) which was deemed safe and efficient in the secondary care domain, was introduced in primary care, a validation study was performed by Oudega et al. In this study the Wells rule was used in combination with a laboratory D-dimer test in primary care.[20] The accuracy of the Wells rule in combination with D-dimer testing was low (21%) and the percentage of missed cases was 2.9%. The data retrieved from this study were used for multivariable logistic regression modeling to quantify combinations of items that contributed to the diagnosis of DVT and to what extent these combinations were able to discriminate between presence and absence of DVT. [21] A new prediction rule was thus created (and later validated) designed especially for use in primary care. The recent introduction of rapid point-of-care D-dimer assays combined with this specific clinical decision rule made it possible to realize a diagnostic work-up entirely in a primary care setting. In this thesis we describe a management study that we conducted in which we investigated the safety and feasibility of patient selection at initial presentation in a primary care facility. (Chapter 4) Subsequently, we assessed whether the decision rule used in the management study needed adjustment based on the new data retrieved from the management study (Chapter 5). Furthermore, we investigated whether or not the approach in which patients could be selected for further examination at first presentation in primary care based on a specialized clinical decision rule and a point of care D-dimer test was deemed cost-effective (Chapter 6). In addition, we describe the characteristics and clinical course of patients from the management study that were *not* diagnosed with VTE but were treated in the context of an alternative diagnosis (Chapter 7).

TREATMENT

In case VTE is diagnosed, anticoagulant treatment has to be installed without delay as thrombosis is a potentially lethal condition. [2] Prevention of a recurrent event is the main objective of anticoagulant treatment for an acute thromboembolic process.

Current management and secondary prophylaxis of venous thromboembolism (Chapter 8) has two major drawbacks. Firstly, during vitamin K antagonist therapy patients need to be monitored closely to maintain efficacy and minimize the bleeding risk due to fluctuations of the prothrombin time (INR). Secondly, after cessation of therapy the problem of recurrent thrombosis arises. Earlier studies have indicated that for most patients vitamin K antagonist therapy aimed at an INR of 2.0 to 3.0 is optimal. For patients with thrombosis due to a temporary risk factor extending treatment beyond 3 months is not needed, while for other patients a minimal duration of one year can be advocated. For patients with cancer (Chapter 9), it is beneficial to postpone therapy with vitamin K antagonist and prolong initial LMWH therapy for 3 to 6 months. [22]

New developments are aimed at further individualization and optimization of the duration of treatment and at the introduction of agents that are suiTable for long term treatment and do not require monitoring.

In our studies we have concentrated on the problem of optimal treatment duration in relation to recurrent events of VTE. The quest for new antithrombotic medication with a more stabile and patient-friendly profile is beyond the scope of this thesis.

RISK INDICATORS FOR RECURRENT THROMBOSIS

The optimal duration of anticoagulant treatment remains a subject of debate [23] due to the inability to identify those at (extremely) high versus those at (extremely) low risk for recurrent thromboembolism. Several strategies can be employed to estimate risk of recurrence, including assessment of amount of residual thrombosis [24, 25], as well as coagulation activity after cessation of antithrombotic therapy by means of laboratory tests such as for D-dimer [26, 27] or FVIII levels. [28-30] However, these laboratory assays reflect ongoing fibrinolysis rather than coagulation (D-dimer), while Factor (F) VIII levels only provide one element of the complex coagulation network. Similarly, determination of FXI, FIX and prothrombin could be utilized as risk indicators, since the levels of these proteins are also associated with risk of venous thrombosis. [31, 32] A more global coagulation test that integrates the information retrieved from separate coagulation tests could potentially improve

patient management. It has indeed been demonstrated that the thrombin generation (TG) assay performed at one point in time is associated with an increased risk of a first episode of DVT in persons with an increased endogenous thrombin potential (ETP). [33] On the other hand, a low chance of recurrence was found in patients after acute DVT with a low ETP. [34]
We therefore explored the possible usefulness of TG for the prediction of individual recurrent thrombosis risk in patients following an event of DVT. In this thesis we describe a study in which we evaluated TG by Calibrated Automated Thrombogram (CAT) in plasma during follow up of 104 consecutive patients after an acute episode of DVT compared to reference plasma derived from healthy individuals. (Chapter 10)
In a second study we assessed the difference in levels of TG between patients with and patients without recurrent VTE. We also assessed the association of known risk factors for VTE with indices of TG. (Chapter 11)

POST THROMBOTIC SYNDROME

Besides the prevention of recurrent thrombosis another challenge in the management of patients after an event of DVT is formed by the prevention of post-thrombotic complaints and the development of the post thrombotic syndrome (PTS).
PTS is a chronic condition that arises in 20-50% of patients following DVT. [35-38] Hence, PTS is the most common complication of DVT. Post thrombotic complaints secondary to acute DVT are thought to be related to venous hypertension caused by venous obstruction or valve destruction. Venous hypertension results in reduced calf muscle perfusion, increased tissue permeability and clinical symptoms typical of PTS. The clinical manifestations of PTS are: pain, edema, skin changes, venous claudication and in severe cases even venous ulcers may occur. The syndrome not only reduces the quality of life [39] but is also responsible for considerable healthcare costs [40] The incidence of PTS has dramatically diminished since the introduction of elastic compression therapy [41, 42] It is however still unclear whether all patients benefit from this therapy to the same extent and whether it is possible to select patients with a low probability for developing PTS based on objective clinical

tests or subjective complaints. We therefore assessed the result of an individualized approach, as was used in our hospital, to the duration of elastic compression therapy on the incidence of PTS in 125 patients after an acute event of DVT. Management was based on systematically recorded clinical symptoms and complaints and reflux as detected by venous duplex ultrasound analyses.

OUTLINE OF THE THESIS

PART ONE

In **Chapter 2** we describe the fundamentals of systematic reviews for consumers of these research articles.

PART TWO

In **Chapter 3** a systematic review of the literature to assess the safety of the exclusion of DVT based on a clinical decision rule and a D-dimer test in a secondary care facility is described.

In **Chapter 4** we describe a large (n=1002) prospective management study that we performed in which triage of patients suspected of DVT was completed entirely in general practice using a work-up based on a simple diagnostic rule combined with a point of care D-dimer test. The strategy combines 7 clinical characteristics plus the result of a laboratory D-dimer test. The strategy discriminates patients unlikely of having DVT from patients with an increased risk of DVT requiring further work-up (AMUSE strategy).

In **Chapter 5** state of the art methodology for updating of clinical prediction rules was used to test whether the accuracy (safety and efficiency) of the diagnostic strategy could be further improved or whether the strategy that was used in the management study represented the optimal algorithm for primary care.

Additionally, in **Chapter 6** the cost-effectiveness of this diagnostic strategy was evaluated as compared to usual care (based either on ultrasound alone or on ultrasound following an in-hospital rule). A Markov model with a five year time horizon was used to compare the costs and effects of the AMUSE strategy to

hospital based strategies. Probabilities were derived from AMUSE and the literature. Societal costs and health state utilities were used.
In **Chapter 7** we describe the fate of the majority of patients initially suspected of DVT. Most of these patients are eventually followed up or treated for their complaints in the context of an alternative diagnosis. We explored the clinical outcomes for these patients.

PART THREE

In **Chapter 8 and 9** two narrative literature reviews are described to assess the current situation concerning the anti-thrombotic therapy in patients diagnosed with VTE and the specific properties of low molecular weight heparin in the antithrombotic therapy in patients with malignancies, respectively.
In **Chapter 10** we describe the results of a study in witch we evaluated the variation in time of thrombin generation between healthy individuals and patients following an acute DVT. We compared on and off anticoagulant treatment on thrombin generation with and without the addition of thrombomodulin (TM). In **Chapter 11** the results of an additional study are presented where patients were followed in time after an acute event of DVT. We investigated whether or not individual levels of thrombin generation were correlated to outcome measures such as recurrent VTE and as a consequence whether thrombin generation could be potentially used as a single predictive test for hypercoagulability. Finally, in **Chapter 12** we assessed whether, after initial compression therapy of 6 months following the acute event, individualized shortened duration of elastic compression therapy has a negative impact on the incidence of PTS.

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Chapter 2

An Overview Of Systematic Reviews

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Glossary	
Review	The general term for all attempts to synthesize the results and conclusions on a given topic
The following features of reviews could be distinguished:	
Narrative review	Authoritative overview on a given topic, based on results and conclusions available in the literature; this category typically does not include a method section and differs from the others in its methodological rigor
Systematic review	When a review strives to comprehensively identify and track down all the literature following a protocol with detailed inclusion and exclusion criteria. The usual intent of this type of review is to provide complete and, if possible, quantitative information.
Meta-analysis	A statistical method to summarize quantitatively evidence from individual studies (most sensible when applied in the context of systematic reviews). Sometimes used as a single term to indicate a quantitative, systematic review that includes a summary statistic as a whole.

INTRODUCTION

The introduction of evidence based medicine has resulted in an increased application of primary research evidence in health care practice and decision making. Reviews that summarize research have become mandatory for coping with the increasing amount of evidence. Narrative reviews historically have been an important tool for information transfer in teaching medicine but their purpose should not focus on making clinical decisions regarding patient care. Such reviews focus on a certain clinical condition or group of conditions, usually sharing a common etiology or group of symptoms, but are not likely to provide unbiased evaluations of management strategies for patient care. Narrative reviews may be useful for introducing learners to any medical subject, as well as for updating clinicians on a (biological) subject of interest. In general, narrative reviews offer a broad view on a subject but are guided by personal interests, opinions and accents. Therefore a high degree of bias can be involved. Narrative reviews have no formal rules other than to give an authoritative overview.

A systematic review however is meant to systematically provide the 'best available evidence' to answer a focused clinical question. Scientific methods and rules do apply for systematic reviews in order to limit bias. As soon as the subject of a review is focused sufficiently to condense it to a single clinical question one should apply the technology available to conduct systematic reviews.

Thus, depending on the situation however either a narrative review or a systematic review can be the best option. When a more comprehensive overview is needed, for instance to understand the biological basis of a disease, the scope of a systematic review can be to narrow and preference can be given to a narrative review. Without the knowledge required to write narrative reviews on a subject, it may be impossible to ask the relevant clinical question that underlies a systematic review. Likewise, without this knowledge it may be impossible to place the result of a systematic review in the context of the usual approach to the condition or disease.

The term *meta-analysis* is often misunderstood. Although meta-analysis is sometimes indiscriminately interchanged with 'systematic review', this is not

appropriate. Meta-analysis applies a statistical method to data retrieved from multiple studies, in order to give a quantitative summary estimate of a (comparative) effect of treatment, for example. Only, if the data retrieved from these studies, were the result of an adequately conducted systematic review, one can consider the effect-estimate resulting from this meta-analysis as representing the best available evidence.

So while the focus of this chapter will be on the science of systematic reviews emphasizing the availability of systematic reviews for clinical decision making, we should realize that in medical education and practice both systematic and narrative reviews have their own appropriate place.

THE CLINICAL QUESTION

The key element of a systematic review in clinical medicine is the formulation of an answerable clinical question. Ultimately, the relevance of the results of a systematic review is determined by the clinical relevance of the question posed. A clinical question is often referred to by the abbreviation PICO (T) [1, 2], which stands for Patient/Population, Intervention, Comparison, Outcome and Time. Each element should be as specific and realistic as possible. Systematic reviews primarily deal with questions regarding interventions. Research questions on other areas such as etiology, diagnosis and prognosis can also be the focus of a systematic review. The framework of PICO (T) still applies but requires modification. A clinically relevant scientific treatment question might thus be the following: “In patients with a carotid stenosis of 50 to 70%, does aspirin, in a daily dosage of 30 to 50 mg compared with a dosage of 600 mg or more, reduce the occurrence of any stroke (ischemic, hemorrhagic or undefined) during treatment periods of one year or longer?”

STRUCTURE OF A SYSTEMATIC REVIEW

Systematic reviews are characterized by a series of steps that should be conducted with a certain methodological rigor. Following the definition of a focused clinical question a comprehensive and exhaustive search of the literature and other sources should then be undertaken to identify potentially

relevant data for the systematic review question. Sometimes multiple searches are required to retrieve all available relevant articles or study reports. To minimize selection bias, at least two independent reviewers must assess the scientific quality of the selected studies. All data should be extracted in the same way and exclusion criteria have to be documented. The validity of combining data should be assessed by looking at possible heterogeneity of outcomes. Homogeneous results can be combined statistically and presented in the form of a meta-analysis. Detailed instructions on how to perform a systematic review are available from a number of sources, in particular the Cochrane Collaboration (www.cochrane.org) [3,4,5] The Cochrane Collaboration an independent, international not-for-profit organization, is dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. The major product of the Collaboration is the *Cochrane Database of Systematic Reviews* which is published quarterly as part of the Cochrane Library.

LITERATURE SEARCH

To identify relevant publications, first search readily available, adequately indexed and regularly updated databases of medical literature, such as Medline, PubMed and EMBASE. However, small, negative trials frequently are not, or they are published only after many perils. Therefore, there is a risk of publication bias, especially if only a limited number of relevant publications can be identified. Publication bias is associated with funnel plot asymmetry. Funnel plots are scatter plots of relative measures of treatment effect (relative risk, odds ratio) plotted on a logarithmic scale on the x-axis and the sample sizes (or standard error) on the y-axis. In the absence of bias the plot should resemble an inverted funnel (see Figure 1). [6]

In particular, if publication bias is surmised, consider additional sources, such as conference abstracts, experts' personal databases, contact with for-profit and non for-profit sponsors, and databases of regulatory authorities. A future source

will be the databases of central medical ethical committees and trial registries such as www.clinical trials.gov.

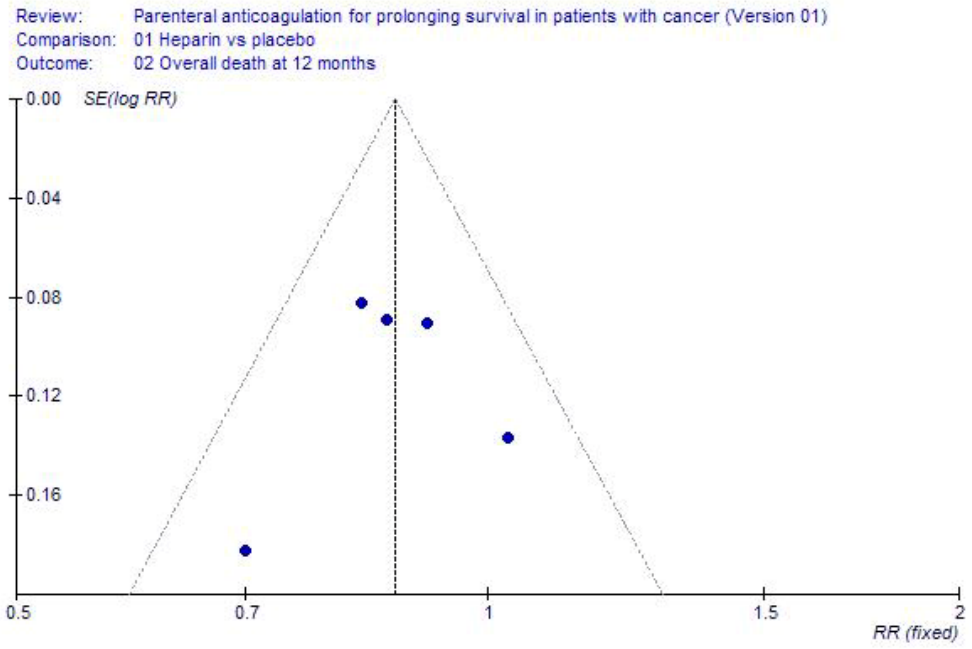

Figure 1. *Inverted funnel plot for randomized controlled trials of parenteral anticoagulation in cancer patients from [6].*

In searching the databases of medical literature, include terms that identify the clinical question of interest as well as some methodological terms related to the type of clinical question of interest. It is accepTable to search relatively narrowly to find a "best article" to answer the clinical question because the best articles are likely to be specifically indexed. For a systematic review a broad search strategy is required because all relevant articles (i.e. bits of evidence) should be identified. The list of obtained references can than be reduced by manually reviewing titles and abstract of articles for which the full text should be obtained, either because they are obviously relevant or because their irrelevance based on the frequently limited information available from title and abstract cannot be decided. The applied search strategy should be reported in detail. The process of manual review should be carried out by two independent researchers and the results of that process made transparent by reporting as described in the QURUM statement [7]. Box 1 reports and example of an adequate search strategy.

Box 1. Example of an adequate search

We searched electronic databases from 1985 until January 2006. These included MEDLINE, EMBASE, Cochrane Library, Google Scholar, epidemiological research Web sites, abstracts of scientific meetings, and bibliographies of relevant studies. The search terms were compiled from the names of individual drugs, the therapeutic class, mode of activity, cardiovascular and cerebrovascular outcome terms, and study design terms. We also searched on authors' names. Titles and abstracts of articles identified by the searches were reviewed by the authors. Searches were repeated using additional search terms identified from articles considered relevant to the review.

From: *McGettigan P, Henry D. Cardiovascular Risk and Inhibition of Cyclooxygenase A Systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2. JAMA 2006; 296:1633-1644.*

SELECTION OF RELEVANT ARTICLES

The selection of studies to be included in the final review should be made based on prespecified criteria for inclusion and exclusion. Usually, the inclusion criteria are directly based on the PICO (T), while the exclusion criteria are based on criteria for minimal methodology criteria (e.g. randomization, adequate population, independent assessment or potential confounding effects). For each excluded study, report the reason for the exclusion.

Naturally, background knowledge of the field can help to adapt the exclusion criteria to an accepTable level. If, for example, the clinical question asked is (expected to be) only addressed in relatively old studies (or as a secondary question) it can be a realistic strategy to allow for clinical controlled trials with a concurrent control group, rather than to limit the acceptance of studies to those "truly randomized with adequate concealment of allocation". The strength of the conclusion and its consequent recommendation should be adapted to the quality of the underlying evidence

ASSESSMENT OF QUALITY

An essential part of the result section of a systematic review is the systematic reporting of essential quality elements in the identified eligible studies. The absence of some quality items might also be used as an exclusion criterion. The choice is usually guided by prior knowledge of paucity or abundance of data in the field. For example, for studies on the prevention of deep-vein thrombosis in orthopedic elective hip surgery, one could be likely to apply some important methodological criterion (e.g. venography assessed unaware of knowledge of treatment allocation) as an inclusion criterion, whereas for studies on the (secondary) prevention of thrombosis in patients with established heparin-induced thrombocytopenia one might be tempted to accept any evidence at hand. However, the latter policy will result in a weaker conclusion. The overall quality of evidence for the question addressed in the systematic review can not surpass the quality of the original studies. Nevertheless, the broader, systematically reviewed evidence will better inform decision makers.

For therapeutic studies, important items of quality include, but are not limited to: randomization, adequate concealment of allocation; blinding (at least for assessment of outcomes); intention-to-treat analysis and reports on all patients.

For diagnostic studies important items of quality include: assessment of the new test independent of knowledge of the result of the reference test; performance of the reference test in all participants; study performance in an adequate population, suspected of disease.

Occasionally, ‘quality scores’ or ‘quality scales’ are used to report on quality of methodology of individual studies. These scales usually honor the presence of a quality item or a reporting item with some points. However, missing points could be due to an extremely relevant missing methodological issue (e.g. adequate concealment of allocation prior to randomization) or to one or more much less relevant issues (e.g. not reporting a power analysis and the fate of two patients in a trial of more than 10.000 patients with an outcome frequency of 10%). Hence, it is more important to focus on individual methodology items of high importance than to trust (and compare) overall quality scores. In fact, lack of usefulness of study level quality scores has been shown [4]. In any case, if a scoring system is used, the scores for the individual items on the scale used

should be provided and results with and without the lower- quality studies should be compared. Usually, two independent researchers assess the quality of individual studies. They discuss any discrepancy in their result (with a third person) to arrive at a consensus conclusion. Extracting data from the individual studies follows a similar process.

PRESENTATION OF DATA AND SUMMARY STATISTICS

A final point is the presentation of the identified data (evidence) and if possible calculation of summary statistics using meta-analysis to assess therapeutic efficacy, harm or diagnostic accuracy. Next to the Table with information on the basic design and methodological quality of the identified studies, a summary presentation showing the results of the individual studies provides important information in a systematic review. In the summary statistics which pools the results of each individual study (meta-analysis), each study can be seen as an individual data point or experiment. These summary statistics should provide both a point estimate and a 95% confidence interval. Figure 2 shows a Forrest plot, one of the frequently used graphic methods to show results of a meta-analysis. [8]

Meta-analysis should only be performed when the results from the identified trials are consistent [7, 9]. Assessing homogeneity can be done by inspection of the graphical display of the individual studies in a Forest plot (see Figure 2). If a significant heterogeneity is found (confidence intervals do not overlap) than the results of the studies should not be pooled. The play of chance should be ruled out by the application of a Chi Square test or the calculation of I^2. I^2 describes the proportion of total variation in study estimates due to heterogeneity rather than sampling error (chance). I^2 ranges from 0 to 100% and a value greater than 50% may be considered substantial heterogeneity and should be explored [10].

Whenever heterogeneity is found to be existent, an explanation for the heterogeneity should be provided. All choices made in a systematic review are based on assumptions and may therefore influence the results. Sensitivity analysis, that is, performing separate pooled analysis after excluding some of the studies (for instance those of lower methodological quality), can show that differences in effect exist between relevant studies.

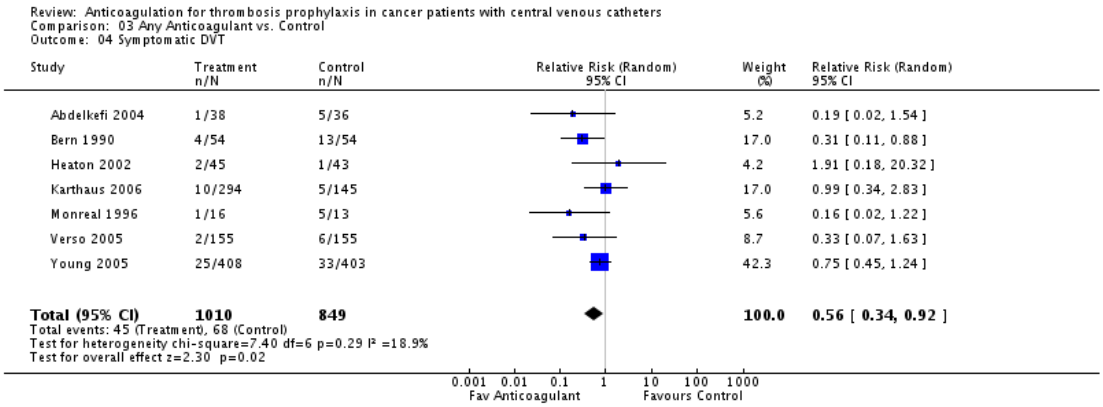

Figure 2. *Forrest plot and meta-analysis results of randomized trials comparing anticoagulant therapy to no therapy for the prevention of deep venous thrombosis related to central venous lines. The plot includes name of the study (identified by the first author and the year of publication), the number of events and patients in the treatment and control group, a graphical representation of the relative risk of each individual study together with the confidence interval, the relative weight of each study contributing to the overall effect measure and the numerical results for each individual study and the overall estimate of effect. The total number of events and results of tests for heterogeneity are also given (see text). From [8].*

CONCLUSION

Systematic reviews are essential for informed health care decisions. They are often quoted as the highest-quality evidence. However, even if a systematic review is conducted according to the highest applicable standards, the evidence included in a systematic review can be weak. Hence, the strength of the conclusion of a systematic review and its use for developing recommendations will have to be based on this underlying quality and consistency of this evidence. For this reason, it is crucial to understand whether a systematic review fulfills basic methodological criteria and what the quality of the underlying evidence is. Furthermore, the main conclusion of a systematic review should be based on the clinical question addressed in the review. Finally, as with all scientific results, this conclusion should be put into the current clinical perspective.

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Chapter 3

Management Studies Using A Combination Of D-Dimer Test Result And Clinical Probability To Rule Out Venous Thromboembolism; A Systematic Review

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J Thromb Haemost. 2005 Nov; 3(11):2465-70.

ABSTRACT

Background: While the number of patients with suspected venous thromboembolism (VTE) referred to hospital emergency units increases, the proportion in whom the diagnosis can be confirmed is decreasing. A more efficient but safe diagnostic strategy is needed.

Objective: To evaluate the safety of withholding anticoagulant therapy in patients suspected of venous thromboembolism based on a diagnostic work-up that combines a clinical decision rule with a D-dimer test result without performing additional diagnostic tests.

Patients/ Methods: We searched Medline (January 1996- December 2004) related articles and reference lists of studies in English for prospective clinical studies that managed consecutive patients suspected of venous thromboembolism and used a D-dimer assay combined with an explicit clinical decision rule or implicit clinical judgment

Results: We identified 11 studies in which 6837 consecutive outpatients suspected of VTE were included. In the combined management studies the overall rate of thromboembolic events was 9 out of 2056 patients (0.44 %, 95% CI 0.2%-0.83%) in whom anticoagulants were withheld based on the D-dimer result and a low clinical score. Similar results were obtained with qualitative and quantitative D-dimer tests and with different decision rules. The rate of exclusion varied between 30% and 50% and was highest with a low prevalence of VTE among those referred.

Conclusion: Withholding anticoagulant treatment in patients suspected of VTE on the basis of a work–up consisting of a low clinical probability combined with either a qualitative or quantitative D-dimer test result is safe.

INTRODUCTION

An increasing number of patients are referred to hospital emergency units with a clinical suspicion of venous thromboembolism [1]. If left untreated, pulmonary embolism can be fatal and deep vein thrombosis can cause considerable morbidity and can eventually result in pulmonary embolism. Treatment with anticoagulants reduces morbidity and mortality [2]. However, unnecessary anticoagulant therapy should be avoided because of the associated risk of bleeding.

The clinical diagnosis of venous thromboembolism is challenging and the diagnosis can be confirmed by the use of objective diagnostic methods only in a proportion of the patients with a clinical suspicion of the disease [3]. Moreover, over the last 20 years this proportion of patients in whom the diagnosis is confirmed has decreased from 35% to 20% [3,4]. This decrease is likely to be attribuTable to a better access to non-invasive testing together with a declining tolerance for diagnostic uncertainty.

In the last two decades, there has been a tendency towards simplification of diagnostic management of venous thromboembolic disease. Although venography and pulmonary angiography remain the gold standards, those tests are in practice seldom used because of their invasiveness. Extensive research has been performed to develop less invasive and more cost effective diagnostic strategies. Serial ultra sonography is a safe approach for the diagnosis of deep venous thrombosis in symptomatic patients [4]. Similarly, CT scan combined with serial ultra sonography has been documented to be safe in the diagnosis of pulmonary embolism [5]. However, the current low prevalence of venous thromboembolism among patients suspected of this disorder renders the approach in which all patients undergo imaging tests costly. Moreover, diagnostic imaging might not always be readily available causing inconvenience to patients due to waiting times.

Although clinical diagnosis is documented to be unreliable the PIOPED investigators showed that clinicians were able to categorize patients by clinical judgement in groups with a low, moderate and high probability for venous thromboembolism. Evaluation of clinical probability scores made evident that clinical probability alone is not sufficient to exclude venous thromboembolism

[6]. Additionally, Clinical Decision Rules (CDR´s) are dependent on experience of the physician certainly when the presence of an unspecified alternative diagnosis is considered.

D-dimer is a fibrin specific degradation product and is used as a marker for endogenous fibrinolysis in D-dimer assays. The safety of relying on a D-dimer test alone to exclude thrombosis is controversial [7] . Only one single study by Perrier et al [8] ruled out pulmonary embolism (PE) on the basis of a D-dimer test alone. A combination of a D-dimer assay and clinical probability as a first step in diagnostic work-up was introduced by Wells et al [9]. Since then multiple studies managing patients with suspected venous thromboembolism on the basis of clinical probability in combination with a D-dimer assay result have been performed.

We included prospective cohort studies in a systematic review assessing the safety and the decrease in need for diagnostic imaging of strategies in which a combination of a CDR together with a D-dimer assay result was used to exclude venous thromboembolism in patients with a negative D-dimer and a low clinical probability. The primary outcome measure was the incidence of objectively confirmed symptomatic venous thromboembolism over a period of 3 months among patients with a normal D-dimer test result and a low clinical probability.

METHODS

We searched pubMed to locate all prospective clinical studies on diagnosis of VTE making use of a combined strategy of D-dimer testing and a Clinical Decision Rule (CDR). We searched Medline for publications from 1996-2004, using the subject headings: (“fibrin”) or (“degradation products”) or (“D-dimer”) and (“pulmonary embolism”) or (“thromboembolism”) or (“thrombosis”) and (“decision rule”) and (“prospective study”) or (“follow-up study”). We also reviewed the reference lists of articles selected and used cross-references from related articles. The authors (MHP, AtC) reviewed all identified titles and abstracts.

The following inclusion criteria were applied: English language, prospective clinical study, consecutive patients, use of D-dimer assay combined with the use of explicit clinical decision rules or implicit clinical judgment, divided in at

least 2 categories. Studies were excluded if they used their data to derive a clinical decision rule, or if management of patients with suspected disease was not only based on results of a D-dimer test and clinical judgment, but was additionally influenced by other test results (e.g. ultrasound).

Data extraction

The following data were extracted: total number of patients included per study, inclusion of only patients suspected of DVT or PE or a mixed population, strategy according to which patients were managed, e.g. normal D-dimer test results and low clinical probability, type of D-dimer test used (qualitative, quantitative), number of patients managed without additional imaging, total number of cases of venous thromboembolism in the population, and thromboembolic outcomes in relation to strategy. Both authors reviewed all data and consensus was reached for all data described.

Analysis

Summary Tables of study characteristics were created. The primary outcome was the 3-month incidence of all thromboembolic outcomes in patients in whom anticoagulant treatment was withheld based on the results of a CDR and D-dimer test. Summary estimates were calculated for all studies, per clinical probability stratum (low, moderate, high), for DVT and PE separately and in relation to type of D-dimer test. Weighted outcome incidences and their 95% CI were calculated using the exact method.

In addition, the overall exclusion rate was calculated and the exclusion rate in individual studies was correlated (Pearson) to the prevalence of VTE in a study.

RESULTS

Study identification

We identified 641 items using our search. Of these 618 were not considered because they did not meet the inclusion criteria. Of the 23 potentially eligible studies using CDR and D-dimer [8, 10-31], 12 had to be excluded, since they were derivation studies or because the management of patients with suspected disease was based on other diagnostic tools for venous thromboembolism than

just CDR and D-dimer [20-31]. Hence, 11 eligible management studies were left for analysis [8,10-19].

All 11 management studies combined CDR with a D-dimer assay test result to exclude venous thromboembolism without further testing in a defined group of people. The majority of studies only excluded patients with low clinical probability together with a normal D-dimer test result from further diagnostic testing [11,13,15-18]. In 3 studies [8,10,12] both the categories low and moderate were managed without further testing. One study excluded unlikely patients [19] and another excluded patients with a non-high clinical probability [14]. We categorized both studies as low clinical probability since both represent a broadening of the low clinical probability group.

Outcomes

The 11 identified studies, included a total number of 6837 patients suspected of venous thromboembolism. All studies were management studies combining CDR and D-dimer assay result to rule out venous thromboembolism without additional diagnostic imaging. All patients were outpatients suspected of either PE or DVT (Table 1).

The overall thromboembolic event rate among patients in whom treatment was withheld based on the clinical probability and a normal D-dimer was 10 out of 2204 (0.45%, 95% CI 0.22 - 0.83%). Of these 10 cases 1 was found in the 143 patients with moderate clinical probability category and a normal D-dimer (0.7% 95 CI 0.02 - 3.8% (Table 2)

The overall thromboembolic event rate when the 2 studies that broadened the low clinical probability group were left out was 6 out of 1810 (0.33%, 95% CI 0.1 - 0.7%).

Patients suspected of PE

We found 4 studies on diagnosis of pulmonary embolism (PE) with a total number of 2760 patients of which 872 (32%) did not have further testing (Table 2). The majority of cases (831) consisted of patients with a low clinical

probability (30%). Perrier et al also declined further testing in 37 patients with a moderate score (1.3%) and in 5 patients with a high clinical score (0.1%). Overall, only one patient (0.1%, 95% C.I. 0.0 - 0.6%) suspected of pulmonary embolism in whom treatment was withheld developed venous thrombo-embolism during a 3 month follow-up period.

Table 1. *Baseline characteristics of studies managing patients on the basis of normal D-dimer test result and CDR alone.*

Study (ref.), year		Patients total	VTE type	Patients in whom additional testing was avoided	Clinical probability	D-dimer test used	Prevalence of VTE in population
Bates [10]	2003	556	DVT	283(51%)	low + mod	MDA	56(10%)
Anderson [11]	2003	1075	DVT	316(29%)	low	simpliRED or IL test	195(18%)
Perrier [8]	2004	965	PE	280(29%)	all	VIDAS	222(23%)
LeClerque [12]	2003	202	MIX	64(32%)	low + mod	TINAQUANT	59(29%)
Wells [13]	2001	930	PE	437(47%)	low	simpliRED	86(10%)
Schutgens [14]	2003	812	DVT	176(22%)	non high	TINAQUANT	317(39%)
Kearon [15]	2001	445	DVT	177(40%)	low	simpliRED	64(14%)
Kruip [16]	2002	234	PE	60(26%)	low	VIDAS	52(22%)
Janes [17]	2001	431	DVT	98(23%)	low	SimpliRED	93(22%)
TenWolde [18]	2004	631	PE	95(15%)	low	TINAQUANT	123(20%)
Wells [19]	2003	556	DVT	218(39%)	unlikely	simpliRED or IL test	87(16%)
Total		*6837*		*2204*			

Patients suspected of DVT

The 6 studies on DVT had a total number of 3875 patients of whom 1268 (33%) did not have additional imaging (Table 2). During the 3 month follow-up period only 9 patients were eventually diagnosed with thrombosis (0.7%, 95% CI 0.3 - 1.3%). The strategy in the DVT group is mainly based on the exclusion of patients with low clinical probability, only 1 study excluded patients with either a low or a moderate clinical probability.

Table 2. *Thromboembolic outcomes over a 3-month follow-up period in patients suspected of VTE managed without anticoagulants based on a normal D-dimer test result and clinical probability.* [1] *Low = non-high,* [2] *Low = unlikely.*

	Study (ref.)	Total thrombo-embolic events	95% C.I.	Strategy		
				Low	Mod	High
PE	Perrier [8]	0/280 (0.0%)	0-1.1%	0/238 (0.0%)	0/37 (0.0%)	0/5 (0.0%)
	Wells [13]	1/437 (0.2%)	0-1.3%	1/437 (0.2%)		
	Kruip [16]	0/60 (0.0%)	0-5.0%	0/60 (0.0%)		
	Ten Wolde [18]	0/95 (0.0%)	0-3.1%	0/95 (0.0%)		
	Total	1/872 (0.1%)	0-0.6%			
DVT	Bates [10]	1/283 (0.4%)	0-2.0%	0/193 (0.0%)	1/90 (1.1%)	
	Anderson [11]	3/316 (1.0%)	0.2-2.8%	3/316 (1.0%)		
	Schutgens [14] [1]	1/176 (0.6%)	0.1-3.1%	1/176 (0.6%)		
	Kearon [15]	1/177 (0.6%)	0-3.1%	1/177 (0.6%)		
	Janes [17]	1/98 (1.0%)	0.3-5.6%	1/98 (1.0%)		
	Wells [19] [2]	2/218 (0.9%)	0.1-3.3%	2/218 (0.9%)		
	Total	9/1268 (0.7%)	0.3-1.3%			
MIX	LeClerque [12]	0/64 (0.0%)	0.0- 4.6%	0/48 (0.0%)	0/16 (0.0%)	
Combined total		10/2204 (0.45%)	0.22-0.83%	9/2056 (0.44%)	1/143 (0.70%)	0/5 (0.0%)

The study performed by LeClerque et al [12] looked at a mixed group of patients, either with PE or DVT, and found that out of 202 patients only 138 needed further testing. The remaining 64 (32%) with either low or moderate clinical probability did not undergo additive testing. Of this entire group no one developed a thromboembolic event over a 3-month follow-up period (0 %, 95% CI 0.0 – 4.6%).

Clinical Decision Rules

The CDR's that were used varied amongst the different investigators. The majority of authors used the Wells score [9, 34]. One of the reviewed studies [18] has applied an adapted Wells score in which there is no division into low, moderate and high clinical probability anymore but only between likely and unlikely. This is due to the fact that from the former moderate probability group

those with a score of 1 are now assigned to new category of "unlikely" while those with a score of ≥ 2 are assigned to the high probability group now known as "likely". A new element of the adjusted score is that 1 point is assigned for a prior history of thrombosis.

The other 2 clinical assessment scores used were the Geneva score and clinical judgment [35] and an intuitive clinical decision model [6].

All decision models that were used have been validated and proved to have comparable predictive values to the more widely used Wells score [6, 36].

Perrier et al [8] made the decision of withholding further testing mainly dependent on D-dimer values.

D-dimer tests

The D-dimer tests used in the 11 selected studies can be divided into quantitative tests, such as MDA, VIDAS, IL test and TINAQUANT and qualitative tests, such as the simpliRED test.

In Table 3 the incidence of thromboembolic outcomes is given according to D-dimer test used (quantitative versus qualitative or mix). All point estimates are low with overlapping 95% confidence intervals. Indeed, these differences are not statistically significant.

Table 3. *The incidence of thromboembolic outcomes over a 3-month follow-up period in patients in whom anticoagulants were withheld, in relation to D-dimer test used.*

Type of D-dimer test	Patients tested	strategy	Number of cases	Overall risk	95% C.I.
simpliRED (qualitative)	712	low	3	0.42%	0.1-1.2%
simpliRED or IL test (mix)	534	low	5	0.94%	0.3-2.2%
MDA, VIDAS,TINA-QUANT (quantitative)	958	low (+ mod)	2	0.21%	0.0-0.8%

Influence of Prevalence

There seems to be a high negative correlation between the prevalence of VTE among referred patients and the proportion of patients who can be managed based on the D-dimer and CDR alone (R=0.71, p=0.014), When the prevalence of the disease in the population is very low (10-16%) the number of patients that

can be excluded from further testing with a strategy that combines a D-dimer assay result and a CDR is between 40-60%. (Table 1).

DISCUSSION

Our analysis that is based on accumulated experience in 6837 patients suspected of venous thromboembolism indicates that triage by a management strategy that combines a CDR with a D-dimer test result is safe. Among patients in whom anticoagulant treatment was withheld based on the CDR and D-dimer results, the overall incidence of thromboembolic events after a 3-month follow-up period was only 0.46%. The approach was safe in both DVT and PE, with 3-month incidences of thromboembolic events of
0.7% and 0.1%, respectively. These results compare favorably to the 3-month incidences obtained in management studies in which all patients underwent testing with reference standards, i.e. venography (1.9%) [37], repeated ultrasonography (0.9%) [38-40], pulmonary angiography (0.8%) [3] or perfusion scanning (1.2%) [25,43-45].

A recent review [41] suggested similar findings. However, this review included only patients suspected of DVT and based its results on a mix of management [10,11,14,15] and derivation studies, [31, 47-50] This latter category of studies is known to produce in general more positive results than validation studies do [51]. Moreover, of the 6 studies that were listed in this review as management studies using a CDR and D-dimer result, 3 performed ultrasonography among all patients according to their method sections [22,26,38], while 3 other large published management studies in patients suspected of DVT that indeed based their management on clinical decision rule and D-dimer results were not identified [11,17,19]. Hence, this review only describes the clinical safety of the novel approach in 1813 patients instead of the 6837 patients in our review.

While the approach can be regarded to be safe in both patients suspected of DVT and PE, the results in this latter group seem far more favorable. Differences in clinical appraisal are unlikely to be the source of this discrepancy, since both the prevalence of thromboembolic disease and the exclusion efficiency are similar in both groups. However, in view of the

potentially higher lethal outcome rate among patients suspected of PE, the finding in itself is comforting.

The use of a combination of a CDR and D-dimer test can lead to a reduction of at least 30% in diagnostic imaging tests. However, in a population with a disease prevalence that is extremely low the reduction may increase to up to 50%. This difference is likely to be due to an increase in the proportion of patients with a low clinical probability in whom the D-dimer testing is also more frequently negative [11].

There is no significant difference in safety between a normal result on a quantitative D-dimer test and a normal result on a qualitative D-dimer test for the exclusion of venous thromboembolic disease in patients with a low clinical probability. This finding is of importance for application in an out of hospital setting where the primary care physician is able to screen suspected patients by using a qualitative D-dimer test. Finally, although a wide array of different CDR's has been used in the studies that have been analyzed, the overall results were highly comparable. The potential disadvantage of a qualitative test is the observer-dependency. Hence, care should be taken to avoid false negative results and the test should ideally be used by experienced personnel only.

CONCLUSION

Withholding anticoagulant treatment in patients suspected of venous thromboembolism on the basis of a work up, consisting of a combination of a CDR and a D-dimer test result, is documented to be safe for the group of patients with a normal D-dimer test result and a low clinical pretest probability score.

By assessing patients according to this strategy, at least a 30% decrease in diagnostic imaging can be achieved. This decrease in diagnostic imaging will result in less waiting time for those patients that need to be tested, and will eventually contribute to diminished costs of health care. For this purpose both quantitative and qualitative D-dimer tests can be used since there were no statistically significant differences in safety. This implies that the primary assessment of patients could even be transferred to an out of hospital setting using a qualitative D-dimer test. This can result in a smaller number of patients

that need to be referred to hospital for additional diagnostic procedures, which will save time and resources for both doctors and patients.

The limitation of this strategy is that it can be safely used only in a very well defined group of patients. Over 50% of patients will still have to undergo a complete diagnostic work-up with an eventually negative outcome.

Studies need to be performed to assess whether a further reduction in diagnostic procedures can be gained safely when also patients with moderate clinical probability are excluded from further testing.

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Chapter 4

Safely ruling out deep venous thrombosis in primary care

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ABSTRACT

Background Up to 90% of referred patients with suspected deep venous thrombosis of the leg do not have this disease.

Objective To evaluate the safety and efficiency of excluding deep venous thrombosis using a clinical decision rule including a point-of-care D-dimer assay at initial presentation in primary care.

Design A prospective management study.

Setting Approximately 300 primary care practices in three regions of the Netherlands (Amsterdam, Maastricht and Utrecht).

Participants 1028 consecutive patients with clinically suspected deep venous thrombosis.

Intervention Patients were managed based on the result of the clinical decision rule including a D-dimer result. Patients with a score ≤ 3 were not referred for ultrasound and received no anticoagulant treatment; patients with a score ≥ 4 were referred for ultrasound.

Measurements The primary outcome was symptomatic, objectively confirmed, venous thromboembolism during 3 months of follow-up.

Results The mean age of the 1028 study patients was 58 years, 37% were males. A valid score was obtained in 1002 patients (98%). In 500 patients (49%) the score was ≤ 3, of who 7 developed venous thromboembolism within 3 months (1.4%; 95% CI 0.6–2.9%). In 502 patients (49%) the score was ≥ 4 and ultrasound was not performed in 3. Ultrasound showed deep venous thrombosis in 125 (25%),for an overall prevalence of 13% (125/1002). Of the 374 patients in whom the ultrasound was normal, 4 developed venous thromboembolism within 3 months (1.1%, 95% CI 0.3–2.7%).

Conclusions A diagnostic management strategy in primary care using a simple clinical decision rule and a point-of-care D-dimer assay reduces the need for referral to secondary care of patients with clinically suspected deep venous thrombosis by almost 50% and is associated with a low risk of subsequent venous thromboembolic events.

INTRODUCTION

Each year more than 140.000 inhabitants of the United Kingdom present to their primary care physician with signs and symptoms suggestive of deep venous thrombosis of the leg.(1,2) As deep venous thrombosis is a potentially life threatening disorder, current practice is merely to refer all these patients for diagnostic testing services. These services are readily available, use non-invasive tests (such as ultrasonography and D-dimer testing) and provide the referring physician with the assurance that a deep venous thrombosis is not missed. (3,4) However, numerous studies have revealed that 80% to 90% of these referred patients do not have deep venous thrombosis.(4-6) Therefore, it would be ideal to safely exclude deep venous thrombosis at initial presentation in a large proportion of these patients and thereby avoid referral.

The recent introduction of rapid point-of-care D-dimer assays that can be included in a specific clinical decision rule makes it possible to realize a diagnostic work-up in a primary care setting.(7,8,10) We recently found that the use of a decision rule – initially developed and validated in secondary care - was not accurate enough for primary care patients suspected of deep venous thrombosis, since the prevalence of thrombosis was still 2.9% among patients with a low probability and a normal quantitative d-dimer as compared to 0.9% in the original publication.(9,10) Hence, we developed and validated such a decision rule specifically for the primary care setting.(9,11) This rule included clinical items and the D-dimer assay result. A major difference between the rules, taken the additional use of D-dimer for low probability patients in the Wells rule into account, is the replacement of the subjective "alternative diagnosis more likely" with the more objective "absence of leg trauma ". The "new" rule had a prevalence of 0.7% (12) of thrombosis in primary care. However, as recently outlined by Reilly and Evans, development and validation studies should be followed by a prospective impact or management study, demonstrating that the rule could be used by physicians to direct care, before the rule is implemented in daily practice.(13)

We, therefore, conducted such a study in a large series of consecutive patients seen in primary care to evaluate the safety and efficiency of excluding deep venous thrombosis by the combination of a clinical decision rule and a point-of-care D-dimer assay. In addition, we determined the yield of ultrasonography in the referred patients.

METHODS

Study overview

In this prospective study in primary care, patients suspected of deep vein thrombosis, were managed using a clinical decision rule that included a point of care d-dimer test. Patients with a low probability of deep vein thrombosis were not referred for further testing and did not receive treatment and were followed for three months to record the incidence of venous thromboembolism. (9,11)

Setting and patients

Affiliated general practices of the three academic centers that were organizing the study were invited to participate. Approximately 300 general practitioners agreed to participate.

From March 2005 to January 2007, consecutive patients who presented with clinically suspected deep venous thrombosis were eligible for the study based on the presence of at least one of three lower extremity symptoms: swelling, redness or pain. Patients were excluded if they were less than 18 years of age, received anticoagulant treatment (i.e. vitamin K antagonists or low molecular weight heparin) at presentation, or were unwilling to participate. Written informed consent was obtained. The study was approved by the local review boards.

Diagnostic strategy

General practitioners applied a clinical decision rule, provided on a worksheet, to all study patients. This clinical decision rule was developed to safely exclude clinically suspected deep venous thrombosis in primary care patients and includes clinical items and a D-dimer assay result (Table 1). (9,11)

As the aim of this study was to improve the management of patients suspected of deep venous thrombosis in a primary care setting, we explicitly selected a rapid point-of-care D-dimer assay (Clearview Simplify D-dimer assay®, Inverness Medical, Bedford, UK).(8,14,15)This facilitated the use of the decision rule by the general practitioner outside office hours and during house calls. A capillary blood sample was drawn by the finger prick method.(14) The test was considered abnormal if, next to the control band, a second band

appeared within 10 minutes.(14) Participating physicians and their assistants received a single brief instruction on the use of the D-dimer assay and the clinical rule.

Physicians calculated for each patient the score using the clinical decision rule (Table 1)(9,11) and patients were managed accordingly. Those with a score ≤ 3 were not referred for ultrasound, received no anticoagulant treatment, but were instructed to contact their general practitioner in case of worsening symptoms. Patients with a score ≥ 4 were referred for ultrasound and received care as usual. Deep venous thrombosis was considered present when (one of) the proximal veins of the lower extremities was non-compressible on ultrasound. (4)

All patients visited their general practitioner between day 5 and 9 for re-evaluation. Three months after entering the study, all patients received a questionnaire addressing signs and symptoms of (recurrent) venous thromboembolism. Non-responders (30%) were contacted, via their general practitioners. If any suspicion of a (recurrent) venous thromboembolic event during the 3 months of follow up, was raised based on this information, additional medical information of patients was retrieved from the general practitioner, including letters from hospital specialists.

Table 1. ***Clinical Decision Rule***[9]***

Variable	Points
Male gender	1
Use of hormonal contraceptives	1
Active malignancy in past 6 months	1
Recent surgery in previous month	1
Absence of leg trauma	1
Distension of collateral veins	1
Difference in calf circumference ≥3 cm	2
D-dimer assay (Simplify) abnormal	6

**If score ≤ 3, no referral for ultrasound;*
If score ≥ 4, referral for ultrasound.

Outcome measure

The primary outcome was defined as the incidence of symptomatic venous thromboembolism during 3 months of follow-up. This included fatal pulmonary embolism, nonfatal pulmonary embolism and deep venous thrombosis. An independent adjudication committee, unaware of the patient's result of the clinical decision rule, evaluated all suspected venous thromboembolic events and all deaths. A diagnosis of pulmonary embolism or deep venous thrombosis was based on a priori defined and generally accepted criteria. (16) Deaths were classified as caused by pulmonary embolism in case of confirmation by autopsy, in case of an objective test positive for pulmonary embolism prior to death, or if pulmonary embolism could not be confidently excluded as the cause of death.(16)

Statistical analysis

Based on an expected incidence of venous thromboembolism during 3 months of follow-up of 1% in patients with a score $\leq$3, and to be able to exclude a predetermined incidence of 4% or more it was calculated that 488 patients needed to be included in this low risk group (type I error 0.05, type 2 error of 0.2). The primary analysis concerned the incidence (with exact 95% confidence interval) of symptomatic venous thromboembolism during 3 months of follow-up in the group of patients with a score $\leq$3 who were not referred for further testing or treatment, and the percentage of patients with this score. Furthermore, we calculated the probability of venous thromboembolism on leg ultrasound at baseline or during follow up, according to the results of the clinical decision rule without the D-dimer assay result as well as to the D-dimer assay result only.

RESULTS

Patients

A total of 1086 consecutive patients with clinically suspected deep venous thrombosis were assessed, of whom 58 (5.3%) were excluded because of predefined exclusion criteria (Figure 1). The characteristics of the 1028 study patients, including the items of the clinical decision rule, are shown in Table 2.

The mean age was 58 years and 37% were males. The suspicion of deep venous thrombosis was based most commonly on leg pain (87%) and leg swelling (78%).

Results of Clinical Decision Rule

In 500 of the 1028 patients (49%) the score was ≤3 and deep venous thrombosis was considered to be ruled out (Figure 1). These patients were not referred for further testing and did not receive anticoagulant treatment. During the 3 month follow up, 7 of these 500 patients developed venous thromboembolism; incidence 1.4% (95% confidence interval 0.6 – 2.9%). Details of these 7 non-fatal events are given in Table 3.

Table 2. *Demographic and clinical characteristics of study population (N=1028)*

Characteristic	Value
Age, mean (SD), years	57.7 (17.1)
Male gender	375 (37%)
Leg complaints	
Pain	874 (87%)
Swelling	784 (78%)
Redness	371 (37%)
Absence of leg trauma	737 (73%)
Varicose veins /venous insufficiency	337 (33%)
Distension of collateral veins	151 (15%
Difference in calf circumference ≥3 cm	304 (30%)
Duration of complaints, median (IQR), days	5 (3-10)
Previous episode of DVT	159 (15%)
Previous episode of PE	51 (5%)
Paresis	13 (1%)
Recent surgery in previous month	81 (8%)
Recent immobilization	75 (7%)
Bed rest > 3 days	72 (7%)
Active malignancy in past 6 months	54 (5%)
Malignancy not treated in the past 6 months	64 (6%)
Use of hormonal contraceptives	107 (10%)
Travel (car/bus/plane) >4 hours	90 (9%)

In 502 of the 1028 patients (49%) the score was ≥4 (Figure 1). An ultrasound was performed in 499 patients and showed deep venous thrombosis in 125 (25%). Of the 374 patients in whom the ultrasound was normal, 4 developed venous thromboembolism during the 3 month follow up period (1.1%, 95% confidence interval 0.3 – 2.7%). Hence, the overall diagnostic parameters for the rule including the D-dimer are a sensitivity of 95%, a specificity of 57%, a positive predictive value of 26%, a negative predictive value of 98.6% and a likelihood ratio of a negative test of 0.09. In 26 patients (2%) the rule was not completed according to protocol (Figure 1). These patients were referred for ultrasound, which showed deep venous thrombosis in 2 (8%).

Table 3. *Clinical details of the 7 patients with score≤ 3 and a venous thromboembolic event during follow-up.*

Patient sex	Age, years	Score on CDR	Positive rule items	Medical history	Time to event, days	Type of event
Male	79	2	Male, absence of leg trauma	Previous TIA, use of anti-platelet drugs	2	DVT popliteal vein
Female	71	3	Vein distension, calf circumference ≥ 3 cm	Previous MI, use of anti-platelet drugs	1	DVT popliteal vein
Female	54	2	Absence of leg trauma, vein distension	None	45	PE
Male	71	2	Male, absence of leg trauma	None	7	DVT popliteal vein
Male	52	2	Male, absence of leg trauma	Previous recurrent VTE	8	DVT popliteal vein
Female	44	2	Use of oral contraceptives, absence of leg trauma	None	13	DVT popliteal vein
Female	52	1	Use of oral contraceptives	None	3	PE

Abbreviations: DVT = deep vein thrombosis; PE=pulmonary embolism; VTE= Venous thromboembolism, TIA=Transient ischemic attack, MI=Myocardial infarction; CDR = clinical decision rule.

Scenario analysis

If one would use only the clinical characteristics of the decision rule and not refer patients with a score ≤3, a deep venous thrombosis would be missed in 9.6% (Table 4). If one would use only the D-dimer assay and not refer patients with normal result, a deep venous thrombosis would be missed in 3.5%. The combination thus reduced this percentage to 1.4%. Patients with a score ≥4 based on clinical items have a probability of deep venous thrombosis of 35.9%. Among these patients, those with a normal D-dimer still have a 23.5% probability of deep venous thrombosis, whereas in those with an abnormal D-dimer this probability increases to 42.6%.

Table 4. *Presence of venous thromboembolism either diagnosed on leg ultrasound at baseline or during the 3 months of follow up in relation to the results of the clinical decision rule without the D-dimer assay result and to the D-dimer assay results itself.*

	N*	N with VTE	Proportion	95%CI
Clinical Items only ≤3	852	82	9.6%	(7-12%)
Clinical Items only ≥4	145	52	35.9%	(28-44%)
D-dimer normal	551	19	3.4%	(2-5%)
D-dimer abnormal	446	115	25.8%	(22-30%)
Clinical Items only ≤3				
D-dimer normal	500	7	1.4%	(1-3%)
D-dimer abnormal	352	75	21.3%	(19-28%)
Clinical Items only ≥4				
D-dimer normal	51	12	23.5%	(13-37%)
D-dimer abnormal	94	40	42.6%	(32-53%)

**In 2 of the 999 complete patients it was unknown whether the score was ≥4 because of the D-dimer assay or clinical items.*
Abbreviations: N = number of patients; VTE = venous thromboembolism, 95%CI= confidence interval.

DISCUSSION

This management study in which physicians actually use the rule to direct their care, shows that primary care physicians can safely rule out deep venous thrombosis in approximately half of their patients by using a simple clinical decision rule including a point-of-care D-dimer test. The observed incidence of venous thromboembolism during three months of follow-up (1.4%; 95% confidence interval 0.6-2.9) compares favourably with that in earlier studies using this strategy in secondary care, as well as with the observed incidence following normal ultrasonography in this study (1.1%, 95% confidence interval 0.3-2.7).(10,17-21) Also, in a worst case scenario were the few patients who were lost to follow-up are considered to have had a VTE event, the two estimates and their 95% Confidence Intervals compare favourably; 1.6% (95% confidence interval 0.7-3.1) after a negative rule and 1.6% (95% confidence interval 0.6-3.5) after a negative ultrasound. Furthermore our findings indicate that performing ultrasonography in the referred patients is efficient, with a confirmed thrombosis in 1 out of 4 patients. The additional benefits are that the burden on diagnostic resources will diminish and that this strategy is more convenient for patients.

Some methodological aspects of our study require comment. First, in total approximately 300 primary care physicians participated. They included a wide spectrum of consecutive patients, both during and outside office hours. The clinical characteristics of the study patients are comparable to those observed in other recent studies conducted in referral centres. Hence, we believe that our findings can be generalised to most patients suspected of deep venous thrombosis. Moreover our strategy proved to be feasible in over 97% of eligible patients (1002 of 1028 patients; Figure 1). The results were obtained in the setting of a true management study and participating health professionals received a single concise instruction at the start of the study only, which suggests a good prospect for implementation in daily practice. The high feasibility with minimal training suggests transferability to other care settings, including night-care.

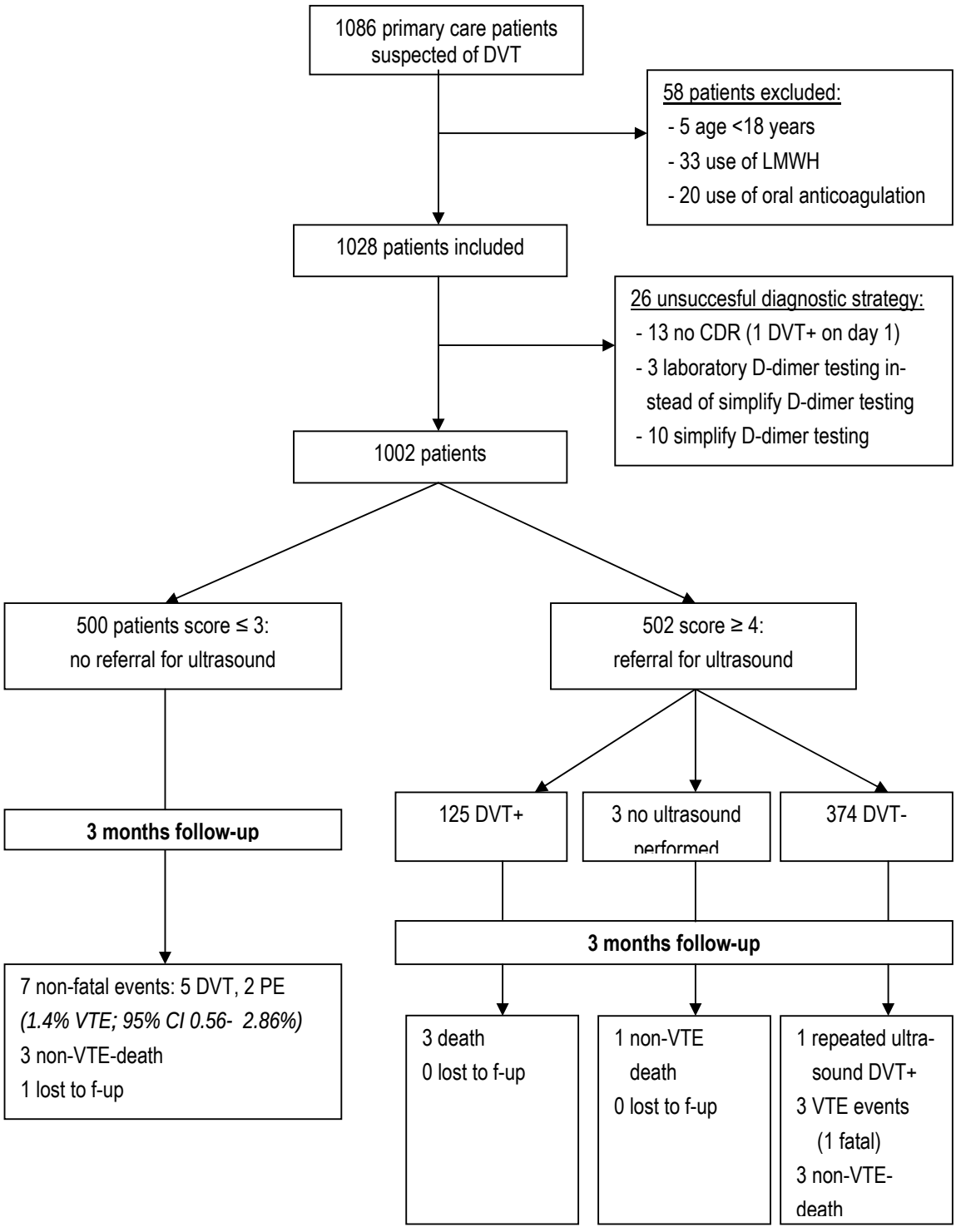

Figure 1. *Study flowchart.*
Abbreviations: DVT = deep venous thrombosis; CDR = clinical decision rule; LMWH = low molecular weight heparin; DVT+ = deep venous thrombosis confirmed by ultrasonography; DVT- = deep venous thrombosis excluded by ultrasonography; VTE = venous thromboembolism; 95% CI = 95% confidence interval; f-up = follow-up

Second, both clinical items and the point-of-care D-dimer test included in the tested strategy are important to rule out deep venous thrombosis, since the number of patients with deep venous thrombosis missed by either component alone is unacceptably high (Table 4). Interestingly, in the presence of a high clinical score (≥ 4), a normal D-dimer result is unreliable, since 24% of these patients will have deep venous thrombosis. This observation, which is in agreement with others, emphasizes that one should refrain from D-dimer testing when the clinical score is high. (6,22) Third, we needed a D-dimer assay that uses capillary whole blood, can be performed in the general practitioners office or at a patient's home and provides an instant and easy interpreTable outcome. As a result, we used a qualitative D-dimer assay.(8, 23) Our results show that the Clearview Simplify D-dimer assay® had a sensitivity of 86% and a specificity of 61% (Table 4). The moderate sensitivity implies that a safe exclusion of deep venous thrombosis can only be reached in patients with a low clinical score (≤3). On the other hand the relatively high specificity results in a good clinical efficiency i.e. a large proportion of patients can be safely spared referral.(24)

Fourth, the clinical decision rule evaluated was specifically designed for and derived in the primary care setting. (9, 11) The present findings underscore the feasibility and safety of this rule. Finally, one potential concern of the introduction of an easily accessible diagnostic test for outpatient use with relatively poor test characteristics is its indiscriminate use as a first test in a testing cascade. However, if such a test is embedded in a strategy that effectively incorporates pre-test probability they can be safely used. The current study and its outcome confirm the usefulness of this approach.

In conclusion, our findings indicate that primary care physicians now have a simple tool available to safely refute the diagnosis of deep venous thrombosis in a large proportion of their patients.

Protocol: available upon request by contacting mh.prins@epid.unimaas.nl

Statistical Code: not available

Data: available upon request, but needs steering committee approval, by contacting mh.prins@epid.unimaas.nl

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Chapter 5

OPTIMIZATION OF THE DIAGNOSTIC STRATEGY FOR SUSPECTED DEEP VEIN THROMBOSIS IN PRIMARY CARE

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Submitted

ABSTRACT

Background: Recently, a simple diagnostic rule was developed for general practitioners to safely discriminate patients unlikely to have DVT from patients with an increased risk of DVT. A large prospective management study, in which general practitioners used this rule to decide which patients suspected of DVT needed referral, revealed very promising results: the number of patient referrals for ultrasound measurements was reduced by almost 50%, at the cost of an acceptably low risk (1.4%) of subsequent venous thromboembolic events in the non-referred patients. However, simple adjustments might further improve the accuracy of the rule; i.e. reduce the proportion of missed diagnoses among non-referred patients (safety) or increase the proportion of patients who do not need to be referred for ultrasonography (efficiency).

Methods: We applied three updating methods to the data of the above mentioned management study, to determine whether adjusting the weights of the included predictors or adding new diagnostic predictors could further improve the accuracy of the rule.

Results: The weights of the eight individual predictors did not need to be adjusted, but inclusion of 'history of DVT' and 'prolonged travelling' significantly added predictive value (p-value < 0.05 using the likelihood ratio test). Although these new diagnostic variables were independent predictors of the presence of DVT, adding these to the rule did not improve the safety and efficiency. In fact, at equal safety (1.4% missed diagnoses among the non-referred patients), the efficiency was lower (43.5%) when using the updated rule compared to the original rule (49.4%).

Conclusion: We concluded that the diagnostic rule for excluding DVT in primary care has optimal accuracy in its original form and does not need any adjustments, providing the final evidence that the original rule can be used to safely exclude clinically suspected DVT in primary care.

INTRODUCTION

Recently, a simple diagnostic rule or strategy was developed for general practitioners to safely exclude clinically suspected deep vein thrombosis (DVT).[1-3] The rule combines 7 clinical characteristics plus the result of a laboratory D-dimer test (Table 1), and was developed to discriminate patients unlikely to have DVT (who would not need additional ultrasonography) from patients with an increased risk of DVT requiring further work-up. With the recent introduction of so-called 'point of care' (POC) D-dimer tests, this diagnostic rule can be completed entirely in primary care. In a large (n=1002) prospective management study, general practitioners actually used the diagnostic rule (Table 1, last column) to decide which patients suspected of DVT needed referral.

***Table 1**. The regression formula and the (simplified) scoring rule of the diagnostic algorithm, developed to exclude clinically suspected deep vein thrombosis in primary care[2].*

Predictors of DVT	Regression formula[a]	Scoring rule[b]
	Regression coefficient	Weight of predictor
Constant	-5.47	
Male Gender	0.59	1
Oral contraceptive use	0.75	1
Presence of malignancy	0.42	1
Recent surgery	0.38	1
Absence of leg trauma	0.60	1
Vein distension	0.48	1
Calf difference ≥ 3 cm	1.13	2
Abnormal D-Dimer test result	3.01	6

[a] The regression formula of the multivariable diagnostic model (as described previously[2]) was:
Risk of DVT presence = 1/(1+exp-(-5.47 + 0.59 *x* male gender + 0.75 *x* oral contraceptive use + 0.42 *x* presence of malignancy + 0.38 *x* recent surgery + 0.60 *x* absence of trauma + 0.48 *x* vein distension + 1.13 *x* calf difference ≥ 3cm + 3.01 *x* abnormal D-dimer test result)).

[b] The weights of the predictors were based on the regression coefficients of the regression formula as described previously.[2] For each patient, a score can be calculated by counting the weights of predictors associated with the characteristics of the patient. According to the scoring rule, patients with scores ≤ 3 do not need to be referred for ultrasonography, in contrast to patients with scores ≥ 4.

The number of patient referrals for ultrasound measurements was reduced by almost 50%, at the cost of an acceptably low risk (1.4%) of subsequent venous thromboembolic events in the non-referred patients.[4] This promising result encourages the use of the diagnostic rule in clinical practice. However, it might well be that adjustment or updating of the diagnostic rule based on the new clinical data could further increase its safety or efficiency, by further reducing the proportion of missed diagnoses among the non-referred patients or increasing the proportion of patients that does not require referral for ultrasonography.

This study assessed - using state of the art methodology for updating of clinical prediction rules [4-7]- whether the accuracy (notably safety and efficiency) of the diagnostic strategy could indeed be further improved or whether the original strategy represents the optimal algorithm for primary care.

PATIENTS & METHODS

Study population

We analyzed the data of the 1,002 consecutive primary care patients suspected of DVT from the above mentioned management study executed between March 2005 and January 2007, among more than 300 general practitioners in three regions in the Netherlands. [8] Patients clinically suspected of DVT, based on the presence of at least one of the following symptoms: swelling, redness or pain of the lower extremity, were eligible for the study. Patients were excluded if they were less than 18 years of age, received anticoagulant treatment (i.e. vitamin K antagonists or low molecular weight heparin) at presentation, or were unwilling to participate. Written informed consent was obtained. The study was approved by the local ethics review boards.

General practitioners systematically documented 32 variables from patient history and physical examination, including the eight predictors from the diagnostic rule and 24 other potential predictors (Table 2). For D-dimer measurement, a rapid POC D-dimer test (Clearview Simplify D-dimer®, Inverness Medical, Bedford, UK),[9,10] was performed, using a capillary blood

sample drawn by the fingerprick method.[11] The test was considered abnormal if, in addition to the control band, a second band appeared within 10 minutes. Participating physicians and their assistants received a brief instruction on the use of the D-dimer test and the diagnostic rule.

***Table 2**. Patient characteristics of the study population (N=1,002). Values are percentages, unless otherwise stated.*

Characteristic	Value
Predictors of the diagnostic rule	
Male gender	37
Oral contraceptive use (% of total women)	17
Active malignancy in past 6 months	5
Recent surgery in previous month	8
Absence of leg trauma	73
Vein distension	15
Calf difference ≥ 3 cm	30
D-dimer test result abnormal	45
Potential additional predictors	
Mean age, years (SD)	57 (17)
Leg complaints Pain	87
Swelling	78
Redness	37
Acutely developed	54
Side of the affected limb, right	49
Median duration of symptoms, days (IQR)	5 (3-10)
History of DVT	16
History of PE	5
History of thrombophlebitis	8
History of any malignancy	6
Immobilization during the previous month	8
Paresis of the leg(s) during the previous month	1
Bedridden during the previous month	7
Known with hereditary coagulation disorder	2
Prolonged travelling (> 4 hours seated)	9
Use of anti-platelet drugs	16
Use of NSAID	12
Pain on palpation	55
Swelling of the whole affected limb	22
Oedema	68
Varicose veins	35
Use of hormonal substitution therapy	4
Pregnancy or post-partum	2
Outcome	
Deep vein thrombosis	14

Physicians calculated for each patient the score using the diagnostic rule (range 0-14; Table 1).[2,3] In accordance with the algorithm, patients with a score ≤ 3 were not referred for ultrasound and received no anticoagulant treatment, while patients with a score ≥ 4 were referred for ultrasound and received care as usual. DVT was considered present when (one of) the proximal veins of the lower extremities was non-compressible on ultrasound.[12]
All patients were evaluated one week ± 2 days after first presentation, and were followed up for 3 months to document all venous thromboembolic events. An independent adjudication committee, unaware of the patient's score of the diagnostic rule, evaluated all deaths and all suspected venous thromboembolic events. This suspicion was based on any symptom potentially indicative of VTE reported by the patient or the physicians who were contacted by the patient. Patients with a venous thromboembolic event within the 3 month follow-up period were considered to have DVT at first presentation.

Methods to enhance the accuracy of the diagnostic rule

To test whether the accuracy of the previously developed diagnostic algorithm (Table 1) could be improved, we applied so-called updating methods to the new data. Several updating methods are available.[4-7] All these methods have to be - and were thus - applied to the underlying regression formula (Table 1, left column) of the diagnostic algorithm.[2] In this formula, which was obtained by using multivariable logistic regression analysis as previously described[2], the risk of DVT is defined as a function of independent predictors of DVT (Table 1):

Log ((risk of DVT) / (1-risk of DVT)) = -5.47 + 0.59 *x* male gender + 0.75 *x* oral contraceptive use + 0.42 *x* presence of malignancy + 0.38 *x* recent surgery + 0.60 *x* absence of trauma + 0.48 *x* vein distension + 1.13 *x* calf difference ≥ 3 cm + 3.01 *x* abnormal D-dimer test result.

The right part of this formula is called the linear predictor and includes the intercept (-5.47; to calculate the risk of DVT when all predictors are absent or zero) and the regression coefficients (relative weights or predictive strength) of the predictors.[4-7,13]

We applied three updating methods, which have all been described extensively and are here briefly explained.[4-7,13] In the first method, both the intercept and regression coefficients of the predictors were adjusted such that the calibration (i.e. the agreement between predicted risks of DVT and observed DVT frequencies) of the regression formula was optimized.[4,5] All regression coefficients were multiplied with a single correction factor that can easily be obtained from the new data (by fitting a logistic regression model with the linear predictor as the only covariate).[4,5] The intercept of the regression formula was then adjusted such that the mean predicted risk was equal to the observed DVT prevalence.[4,5] Updating method 1 will not influence the proportion of missed diagnoses among non-referred patients (safety) or the proportion of patients not requiring referral for ultrasonography (efficiency). This is because all regression coefficients of the rule are equally adjusted such that the relative ranking of the patients in DVT versus no DVT is not altered. Only the calibration of the rule may improve. However, this recalibration was necessary as the two following updating methods – aimed at improving the rule's safety and efficiency – build on this first updating method.

Updating method 2 was used to determine whether the strength (i.e. regression coefficient) of each of the 8 predictors in the new data was similar to the strength of the predictors in the data in which the rule was originally developed. Individual regression coefficients that were significantly different in the new data (defined by a p-value < 0.05 using the likelihood ratio test) were re-estimated or adjusted.

With updating method 3, we evaluated whether one or more of the other potential predictors (Table 2) that were not included in the original rule but documented in each study patient provided additional diagnostic accuracy, such that they had to be added to the original. For each potential predictor, the added accuracy was tested by adding each potential predictor individually to the regression formula. If the regression coefficient of a potential predictor had a p-value < 0.05 (using the likelihood ratio test) the variable was considered to significantly add to the original regression formula and was included (using forward selection starting with the potential predictor with the smallest p-value).

All newly estimated regression coefficients (method 2 and 3) were finally shrunk to prevent overfitting.[4,5,14] Analyses were performed by using R version 2.5.1.

Accuracy of the updated rule

After applying the above updating methods to the underlying regression formula of the original rule, each updated rule was again transformed to an easy to use updated diagnostic (scoring) rule – using the same methods as applied for the original rule (see Table 3, legend).[2] We then studied whether we could define a score threshold at which the updated simplified scoring rule had an improved accuracy compared to the original scoring rule of Table 1. Because the rule was initially developed to safely exclude suspected DVT, relevant accuracy measures of this rule were the *efficiency* of the rule (i.e. proportion of patients with a score below the threshold, who were thus not referred for ultrasonography) and the rule's *safety* (i.e. its ability to minimize the proportion of DVT cases among the patients with scores below the threshold).

Additionally, we determined the proportion of patients in whom the clinical characteristics of the final rule (without a D-dimer test result) already provided sufficient diagnostic information to determine whether patients needed to be referred for ultrasonography.

Missing data

An average of 3.3% of the values for the potential predictors was missing. Missingness of data seldom occurs completely at random. Deleting subjects with a missing value does not only lead to a loss of statistical power, but often also to biased results. Therefore, imputing missing values is generally preferred to complete case analysis.[15-18] Missing data were thus (single) imputed with values obtained from regression equations using SPSS version 14.0 (SPSS, Inc., Chicago, Il, USA).

RESULTS

The characteristics of the 1,002 study patients, including the items from the original rule and all potential additional predictors, are shown in Table 2. The

mean age was 57 years and 63% was female. DVT was present in 136 (13.6%) patients.

Table 3. Regression coefficients of the original and updated regression formula and weights of the original and updated simplified scoring rule.

Predictors of DVT	Original		Updated	
	Formula, regression coefficient	Diagnostic rule, weight of predictor	Formula, regression coefficient	Diagnostic rule, weight of predictor[a]
Constant	-5.47	-	-4.58	-
Male Gender	0.59	1	0.44	1
Oral contraceptive use	0.75	1	0.56	1
Presence of malignancy	0.42	1	0.32	1
Recent surgery	0.38	1	0.29	1
Absence of leg trauma	0.60	1	0.45	1
Vein distension	0.48	1	0.36	1
Calf difference ≥ 3 cm	1.13	2	0.85	2
Abnormal D-Dimer test result	3.01	6	2.27	6
Prolonged travelling (> 4 hours seated)	-	-	0.73	2
History of DVT	-	-	0.64	2

[a] *The weight of the predictors were obtained by dividing the regression coefficient by 0.4. These Figures were subsequently rounded to the nearest integer.*

Updating of the diagnostic rule

None of the eight individual predictors of the original rule (Table 1) showed a significantly different effect in the new data compared to the data in which the rule was developed (updating method 2). P-values of the likelihood ratio tests varied from 0.73 for the predictor 'vein distention' to 0.12 for 'abnormal D-dimer test result'.

Updating method 3 yielded that two of the other potential predictors (Table 2) had significant added diagnostic value in the new data ('history of DVT', p-value 0.014 and 'prolonged travelling', p-value 0.023). Hence, these two predictors were added to the original rule. This new updated regression formula was then transformed to an updated scoring rule (Table 3). Because two predictors were added, the possible score range of the updated diagnostic rule was wider (0-18) compared to the original diagnostic rule (0-14). Applying a score of ≤ 3 to decide upon further work-up, the updated scoring rule excluded

DVT in 43.5% of the patients (efficiency), of whom 1.4% had DVT (safety), compared to 49.4% and 1.4% by the original scoring rule, respectively (Table 4). After increasing the threshold of the updated rule to 4 (i.e. non-referral for scores ≤ 4), the rule's efficiency increased to 51%, at the cost of a safety of 2.9%. As expected, safety worsened further if higher thresholds for non-referral were applied to the updated scoring rule. Also when using a threshold for non-referral below 3, the updated diagnostic rule did not yield better results than the original diagnostic rule (Table 4).

Table 4. *Safety and efficiency of the original (Table 1) and updated (Table 3) diagnostic scoring rule. Values are given in percentages.*

Score threshold	Original Diagnostic scoring rule			Updated diagnostic scoring rule		
	Efficiency[a]	Safety[b]	n DVT / n below threshold	Efficiency[a]	Safety[b]	n DVT / n below threshold
≤ 1	24.2	0.4	1 / 242	18.1	0.6	1 / 181
≤ 2	42.0	1.4	6 / 421	33.4	1.5	5 / 335
≤ 3	49.4	1.4	7 / 495	43.5	1.4	6 / 436
≤ 4	53.2	3.4	18 / 533	51.0	2.9	15 / 511
≤ 5	54.6	3.7	20 / 547	53.3	3.0	16 / 534
≤ 6	57.2	4.0	23 / 573	56.0	3.9	22 / 561
≤ 7	67.1	5.8	39 / 672	63.8	5.0	32 / 639
≤ 8	80.7	8.9	72 / 809	74.7	6.6	49 / 748
≤ 9	90.2	10.5	95 / 904	84.2	8.1	68 / 844
≤ 10	97.4	12.5	122 / 976	93.3	11.1	104 / 935
≤ 11	99.6	13.4	134 / 998	97.0	12.6	122 / 972
≤ 12	100	13.6	136 / 1002	98.9	13.2	131 / 991
≤ 13				99.9	13.6	136 / 1001
≤ 14				99.9	13.6	136 / 1001
≤ 15				100	13.6	136 / 1002

[a]Efficiency: proportion of patients with a score below the threshold of the scoring rule (non referral patients). [b]Safety: proportion DVT among non referral patients. n = number of patients .

Final diagnostic strategy

In view of the findings presented above and given the focused use of the diagnostic rule, i.e. to safely and as efficiently as possible exclude clinically suspected DVT in primary care, we decided that the original rule required no

further updating. A disadvantage of the original rule is that in each patient a (POC) D-dimer test had to be executed. Table 5 shows that in patients with a score of 4 points or more based on the clinical characteristics only, the risk of DVT was 35.3%, which decreased to 23.6% with a normal D-dimer test result and increased to 42.1% with an abnormal D-dimer test result. Thus, D-dimer testing is of limited value in patients with a clinical score (based on clinical characteristics only) exceeding 3 and could be restricted to patients with a clinical score ≤ 3. Figure 1 reflects this suggested strategy for primary care practice.

Table 5. *Presence of deep vein thrombosis (DVT) in relation to the results of the original scoring rule (Table 1) without the D-dimer test result and to the D-dimer test result itself.*

	DVT absent, n	DVT present, n	Total, n (% DVT)
Clinical Characteristics only ≤ 3	767	82	849 (9.7%)
D-dimer normal	488	7	495 (1.4%)
D-dimer abnormal	279	75	354 (21.2%)
Clinical Characteristics only ≥ 4	99	54	153 (35.3%)
D-dimer normal	42	13	55 (23.6%)
D-dimer abnormal	55	40	95 (42.1%)
D-dimer unknown*	2	1	3 (33.3%)

** The contents of this Table are based on the unimputed data. All data was available apart from 3 D-dimer test results in patients with scores ≥ 4 based on only the clinical characteristics of the rule. The reason for not performing the D-dimer test was because these patients were referred anyhow as the score was already larger than 3 without the test. n = number of patients.*

DISCUSSION

We studied whether the accuracy of a recently developed diagnostic rule to safely exclude clinically suspected DVT could be further improved by adjusting the weights of the included predictors or by adding new diagnostic predictors. The weights of the eight individual predictors did not need to be adjusted, but inclusion of 'history of DVT' and 'prolonged travelling' significantly added predictive value. Although these new diagnostic predictors were statistically contributing to the prediction of the presence or absence of DVT and may improve the accuracy of the predicted risks on a continuous scale (0-100% risk

of DVT), adding these to the rule did not confer clinically relevant effects. After introducing a threshold used in practice to determine which patients need to be referred to secondary care, the safety and efficiency of the updated rule did not improve for any score threshold. In fact, at equal safety (1.4% missed diagnoses among non-referred patients), the efficiency of the updated rule was lower (43.5%) compared to the original rule (49.4%). The diagnostic contribution of the two additional predictors was apparently not around the score thresholds 3 to 5.

Our data further indicate that physicians may refrain from performing D-dimer testing in patients with a score of 4 points or more based on the clinical characteristics of the rule only (i.e. in 15% of all patients suspected of DVT). In these patients, the risk of having DVT is still high (23.6%) when the D-dimer test result is normal; they should be referred for ultrasonography regardless of their D-dimer level. To reduce both the number of ultrasounds and D-dimer tests in suspected DVT in primary care, we therefore propose the strategy as shown in Figure 1.

A few methodological issues should be discussed. First, different reference standards were used, depending on a patient's score. According to the protocol, patients with a score ≤ 3 were not referred for ultrasonography, in contrast to patients with scores above this threshold. However, all patients were followed for three months to document all possible cases of venous thromboembolism. Such a three month follow up period is commonly used in studies on the diagnosis of DVT.[19,20] It is assumed that if a thrombus were present at first presentation, this would have been clinically identified within this follow-up period. Therefore, bias due to differential verification (use of different reference standards) was unlikely. Second, by using our large database of patients suspected of DVT, we tested whether the effect of the 8 predictors included in the rule should be adjusted and we explored the added predictive value of a large number (i.e. 24) other possible predictors. Since we used an alpha of < 0.05 to indicate statistical significance, which is associated with a 1 in 20 risk of finding spuriously significant results, 1 or 2 spuriously significant results can be expected. The possibility that the two significant results we found were false-positives is of limited importance only, because adding these two potential

predictors to the diagnostic rule did not improve the rule's safety or efficiency anyhow.

In conclusion, the recently developed diagnostic rule for excluding DVT in primary care has optimal accuracy and does not require any adjustments. In addition to previously performed validation studies, the result of this study may provide the final evidence that the diagnostic rule can be used to safely reduce the number of ultrasound and D-dimer measurements in primary care patients clinically suspected of DVT.

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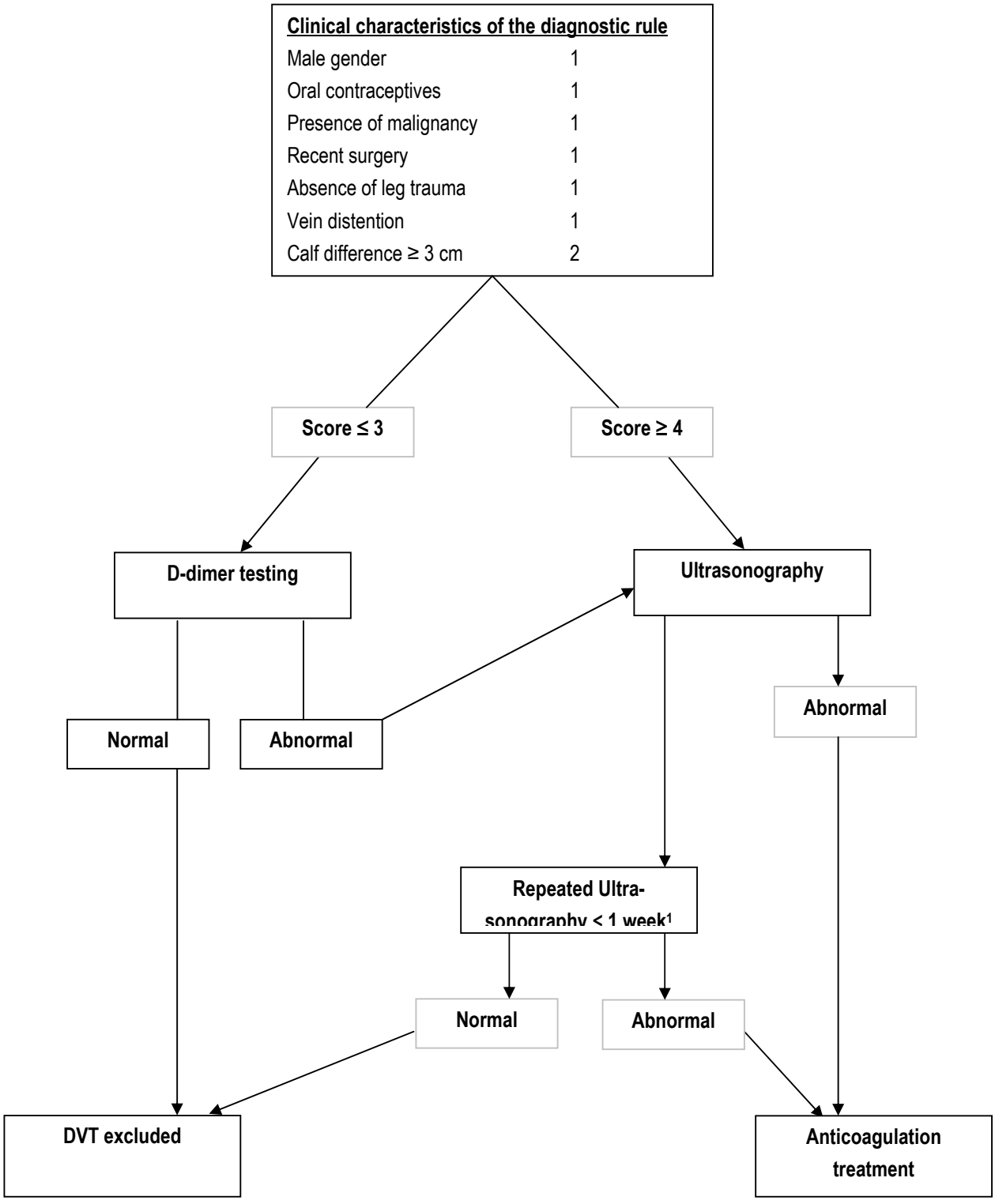

Figure 1*. Proposed diagnostic strategy for safely excluding deep vein thrombosis in primary care.*

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CHAPTER 6

Cost-Effectiveness Of Ruling Out Deep Venous Thrombosis In Primary Care Versus Care As Usual

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Submitted

ABSTRACT

Background: The timely diagnosis of DVT is critical because this disorder can be life threatening. However, referring all patients suspected of DVT for ultrasound testing is inefficient since 80 to 90% of those referred have no DVT. Therefore, we investigated the cost-effectiveness of a diagnostic strategy based on a point of care d-dimer test combined with a clinical decision rule that was documented to be safe in primary care (AMUSE).

Methods: A model based cost-effectiveness analysis was conducted in conjunction with a recent multi centre prospective diagnostic study (AMUSE, N=1002). A Markov model with a five year time horizon was used to compare the AMUSE strategy to hospital based strategies. Probabilities were derived from AMUSE and the literature. Societal costs and health state utilities were used. One way and probabilistic sensitivity analyses were conducted. Cost-effectiveness acceptability curves were constructed.

Results: The AMUSE strategy had both slightly lower costs and less QALYs than both care as usual strategies. We compared the AMUSE strategy to the best hospital strategy. This resulted in a saving of € 138, and a QALY loss of 0,002. The iCER is € 56.436. The cost-effectiveness acceptability curves show that the AMUSE strategy has the highest probability of being cost-effective, even exceeding ceiling ratios over € 80.000.

Conclusion: The AMUSE strategy to exclude DVT in primary care is not only safe, but also cost-effective as compared to hospital based strategies, with or without a rule, to diagnose DVT.

INTRODUCTION

As deep venous thrombosis (DVT) is a potentially life threatening disorder, current practice is to refer all these patients for objective testing to specialized diagnostic services. These services are readily available, use non-invasive tests (such as ultrasonography and D-dimer testing) and provide the referring physician with the assurance that a deep venous thrombosis is not missed [1, 2] However, numerous studies have revealed that 80 to 90% of these referred patients do not have deep venous thrombosis [2,3]. Therefore, it would be ideal to safely exclude deep venous thrombosis at initial presentation in a large proportion of these patients and thereby avoid referral, and hence save costs.

The recent introduction of rapid point-of-care D-dimer assays combined with a specific clinical decision rule makes it possible to realize a diagnostic work-up in a primary care setting [4, 5,6]

In a recent management study in a large series of consecutive patients seen in primary care, the safety and efficiency of excluding deep venous thrombosis by the combination of a clinical decision rule and a point-of-care D-dimer assay, was evaluated. The clinical decision rule that was used was derived from earlier studies in primary care [6], but was not yet validated in a true management study before. The results of the management study that was recently performed did not indicate the need for recalibration of the rule [7]. The findings of this management study indicate that primary care physicians now have a simple tool available to safely refute the diagnosis of deep venous thrombosis in a large proportion of their patients.

This present study focuses on the cost-effectiveness of a diagnostic strategy as evaluated in the above mentioned management study, as compared to usual care (based either on ultrasound alone or on ultrasound following an in-hospital rule).

METHODS

Model description

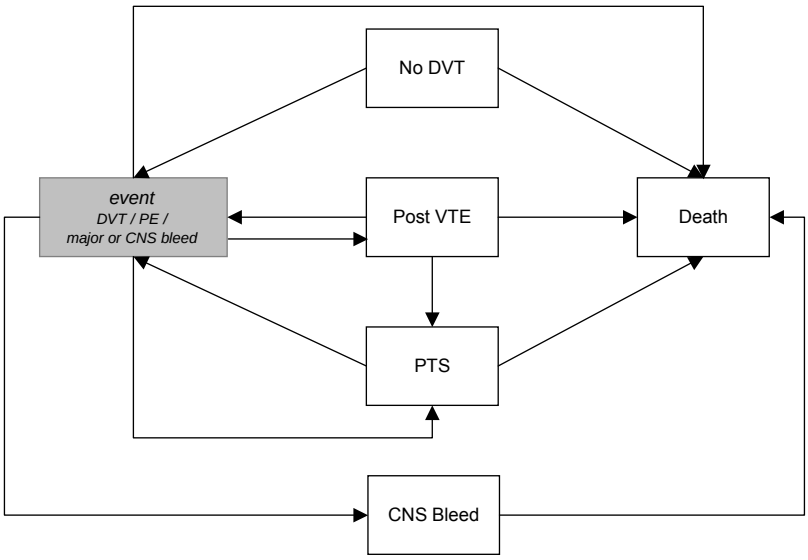
A Markov model was constructed with mutually exclusive health states. The model simulated the course of events in a hypothetical cohort of 1002 persons who present to their primary care physician with signs and symptoms suggestive of DVT of the leg (equal to the cohort included in the prospective study). First order Monte Carlo simulation was not feasible because patient characteristic dependent probabilities were not available for the alternative diagnostic strategies. In the model, as time progresses, persons move between the different health states according to a set of transition probabilities. The cycle length of the model was set to six months, with a 5 year time horizon. The model was constructed to compare the expected 5-year costs and health effects of different diagnostic strategies for suspected DVT. The following diagnostic strategies were compared:

AMUSE rule in primary care, followed by ultrasound in hospital for patients with a score of 4 and higher (referred to as *AMUSE rule*).

Referral to the hospital with ultrasound for all patients (referred to as *Hospital*).

Referral to the hospital with Wells rule in hospital followed by ultrasound for patients with a Wells score of 2 and higher (referred to as *Hospital rule*).[8]

Figure 1. *Model structure*



Model construction

Health states

Health states in the model were: no history of DVT, post venous thromboembolism (Post VTE), post thrombotic syndrome (PTS), and central nervous system bleeding (CNS bleed). The probability of recurrent VTE is higher for persons that have experienced a prior event of VTE compared to the population risk; therefore the health state Post VTE was included in the model. The health states PTS and CNS bleed were included because these conditions cause disutility and costs. The following events were modelled: DVT, pulmonary embolism (PE), major (gastrointestinal) bleed and CNS bleed. The final absorbing state was Death. Figure 1 is a graphical presentation of the model structure.

Model assumptions

It was assumed that every patient with DVT or recurrent episodes of DVT and PE was treated for six months with anticoagulant medication. The costs and consequences of the events DVT, PE, major bleed, and CNS bleed are calculated for six months, after this period persons move to one of the health states: post VTE, PTS, CNS bleed, or Death.

Probabilities

The probabilities associated with the diagnostic strategies and the consequences of treatment for VTE are given in Table 1. Data were derived from the prospective study (AMUSE), as well as from the literature. Background mortality was based on age-specific death rates from the Central Bureau of Statistics.

Table 1. *Transition probabilities.*

Parameter	Mean	SE	Distribution	Source
Prevalence VTE first cycle	0,14	0,01	beta	AMUSE [6]
Ratio complaint to event	0,14	0,01	beta	AMUSE
Sensitivity AMUSE strategy	0,9265	0,0223	beta	126/136; AMUSE
Positive AMUSE rule	0,5010	0,0158	beta	AMUSE
Sensitivity hospital strategy	0,9770	0,0160	beta	85/87; Wells, 2003[9]
Sensitivity hospital rule strategy	0,9692	0,0061	beta	787/812; Meta-analysis[1]
Positive hospital rule	0,8182	0,0164	beta	Ten Cate-Hoek, 2005[3]
PTS	0,03	0,01	beta	Prandoni, 1996 [10]
Major bleed in treated patients	0,0210	0,0014	dirichlet	Linkins, 2003 [11]
Fatal bleed in treated patients	0,0034	0,0006	dirichlet	Linkins, 2003
CNS bleed in treated patients	0,0012	0,0003	dirichlet	Linkins, 2003
Fatality of PE in treated patients	0,43	0,07	beta	Douketis, 1998[12]
Population risk event VTE	0,001	0,0001	beta	White, 2003[13]
Recurrent VTE	0,03	0,01	beta	Prandoni, 1996[10]
PE given VTE	0,27	0,13	beta	AMUSE [6]

The meta-analysis of Ten Cate-Hoek, 2005 was extended with data from the contributing studies: [4],[9][14-17].

Health effects

The health state utilities assigned to the different health states and events are presented in Table 2. The disutility from having PTS and from experiencing an event DVT was calculated from EQ5D data in the prospective study. The quality of life of persons in the health states No DVT and Post VTE was assumed to be equal to the quality of life of persons in the general population. As utility weights age specific EQ5D norm values for the general population were used [18]. For the events PE and major bleed and the health state CNS bleed Time Trade Off values from the literature were used. [19, 20]

Table 2. *Utilities and disutilities for health states and events.*

Utilities		Mean	SE	Distribution	Source
health states					
No DVT & Post VTE				beta	Age specific norm values,
	18-19	0.94	0.02		Kind, 1999 [18]
	20-24	0.94	0.02		
	25-29	0.93	0.03		
	30-34	0.93	0.03		
	35-39	0.91	0.04		
	40-44	0.91	0.04		
	45-49	0.85	0.04		
	50-54	0.85	0.04		
	55-59	0.80	0.04		
	60-64	0.80	0.04		
	65-69	0.78	0.04		
	70-74	0.78	0.04		
	75-79	0.73	0.04		
Disutility PTS		0.02	0.03	beta	AMUSE[6]
CNS Bleed		0.33	0.01	beta	Van Dongen, 2004 [19]
events					
Deep Venous Thrombosis		0.67	0.03	beta	AMUSE [7]
Pulmonary Embolism		0.62	0.01	beta	Van Dongen, 2004 [19]
Major bleed		equal to pulmonary embolism			Based on Locadia, 2004 [20]

Costs

All unit costs were based on actual costs or standard unit costs from the Dutch Cost Manual [21] Volumes of medical consumption were based on the prospective study, the literature, as well as on expert opinion. In Table 3 the mean costs for the three diagnostic strategies and for the health states and events are listed.

The costs of the strategies included the costs of medical care and travel costs to the GP and/or the hospital. In the AMUSE strategy two GP consultations, the d-dimer point of care test, GP time to perform d-dimer testing, and, in case of referral based on a positive rule, ER visit, ultrasound, and in-hospital lab procedures were included. In the hospital strategy only one GP consultation was included, while all patients received an ER visit and ultrasound. In the hospital rule strategy the ultrasound was limited to patients with a positive rule including

a hospital d-dimer test. It was assumed that persons in the health states No DVT and Post VTE did not experience any costs related to DVT. Persons in the health state PTS and CNS bleed did experience costs. To calculate the costs of diagnosing DVT after the initial presentation of complaints (in the following Markov cycles), the incidence of VTE as found in the literature was multiplied by the ratio complaint to documented VTE as observed in the prospective study. Details of the costs calculations are listed in the Appendix.

Table 3. *Summary of cost parameters per cycle of 6 months or per event.*

Parameter	Mean value	Sources	Uncertainty
Diagnostic strategies			
AMUSE strategy	€ 168	Various, see appendix	Fixed
Hospital strategy	€ 251	Various, see appendix	Fixed
Hospital rule strategy	€ 227	Various, see appendix	Fixed
Travel for diagnosis			
Travel to GP	€ 3	Various, see appendix	See appendix
Travel to hospital	€ 7	Various, see appendix	See appendix
Health states			
PTS	€ 3,247	Various, see appendix	minimum € 140, maximum € 10,580[1]
CNS bleed	€ 28,419	Costs of nursing home admission	Fixed
Events			
Incident PTS	€ 3,367	Various, see appendix	minimum € 273, maximum € 10,670[1]
DVT	€ 1,322	Various, see appendix	See appendix
PE	€ 4,210	Various, see appendix	See appendix
Major bleed	€ 4,211	Various, see appendix	minimum € 1688, maximum € 11,497[1]
CNS bleed	€ 11,281	Bergman et al, 1995	Fixed

[1] *A beta pert distribution was used in the probabilistic sensitivity analysis*

ANALYSIS

We compared the cost-effectiveness of three diagnostic strategies: the AMUSE strategy, the hospital strategy and the hospital rule strategy. Incremental cost-effectiveness ratios (iCERs) were calculated, dividing the incremental costs by the incremental QALYs. ICERs were calculated by comparing each strategy

with the next most effective strategy. Whether a strategy is deemed efficient depends on how much society is willing to pay for a gain in effect, which is referred to as the ceiling ratio. In the Netherlands an informal ceiling ratio of €80,000 per QALY exists. [23] This is however a maximum ceiling ratio which applies when there is a high burden of disease. Although this, may not directly apply to DVT, the complications of (missed) DVT, such as PE and PTS, and the side-effects of the treatment of DVT, like CNS bleed, can be considered as serious conditions. The National Institute for Health and Clinical Excellence in the United Kingdom uses a ceiling ratio between £20 000 and £30 000 per QALY [24], which is roughly €40 000.

Uncertainty surrounding the iCERs was handled probabilistically. This means that we assigned distributions to the model parameters, to reflect the second-order uncertainty in the estimation of that parameter. [25] Measures of variance were retrieved from the prospective study, the patient cohort or published literature and, if no other source was available, from expert opinion. See Table 1 for the assigned distributions. Parameter values were drawn at random from the assigned distributions, using Monte Carlo simulation with 1000 iterations. To illustrate the results of the simulation, cost-effectiveness acceptability curves (CEACs) were calculated. [26, 27] For different ceiling ratios, the net monetary benefit was calculated for each strategy by subtracting the costs from the effects, multiplied by the ceiling ratio. CEACs show the probability that a pathway has the highest net monetary benefit, and thus is deemed cost-effective, given different ceiling ratios.

Costs were calculated to their 2004 value using price index Figures form the Central Bureau of Statistics. Future costs and effects were discounted to their present value by a rate of 4% and 1.5% respectively, according to Dutch guidelines. [28]

The base case analysis was based on the observed age (58 years) and sex distribution (375 males; 37 %) as well as the proportion of patients with PTS (62; 6%) and previous VTE (170; 17 %) in the prospective study.

Sensitivity analyses were performed to test the consistency of the results. Included in the one-way sensitivity analyses were the discount rate and age, as well as the following (partially) fixed cost parameters: the health states PTS and

CNS bleed, and the events DVT, PE, major bleed and CNS bleed. Furthermore, we calculated the costs and the sensitivity of the AMUSE diagnostic strategy for iCERs of € 40,000 per QALY.

RESULTS

Base case analysis

The AMUSE strategy had both slightly lower costs and less QALYs than both care as usual strategies. The hospital strategy was the most effective, and had the highest costs. The iCER of the hospital strategy versus the hospital rule strategy amounts to € 91,057. This indicates that, even based on a maximum threshold of € 80,000, the hospital rule strategy is to be preferred. Therefore, we compared the AMUSE strategy to the hospital rule strategy. This resulted in a cost saving of € 138, and a QALY loss of 0,002. The iCER is € 55,753. If usual care consists of an equal mix of the hospital and hospital rule strategy, the iCER of the AMUSE strategy is € 58,662. See Table 4.

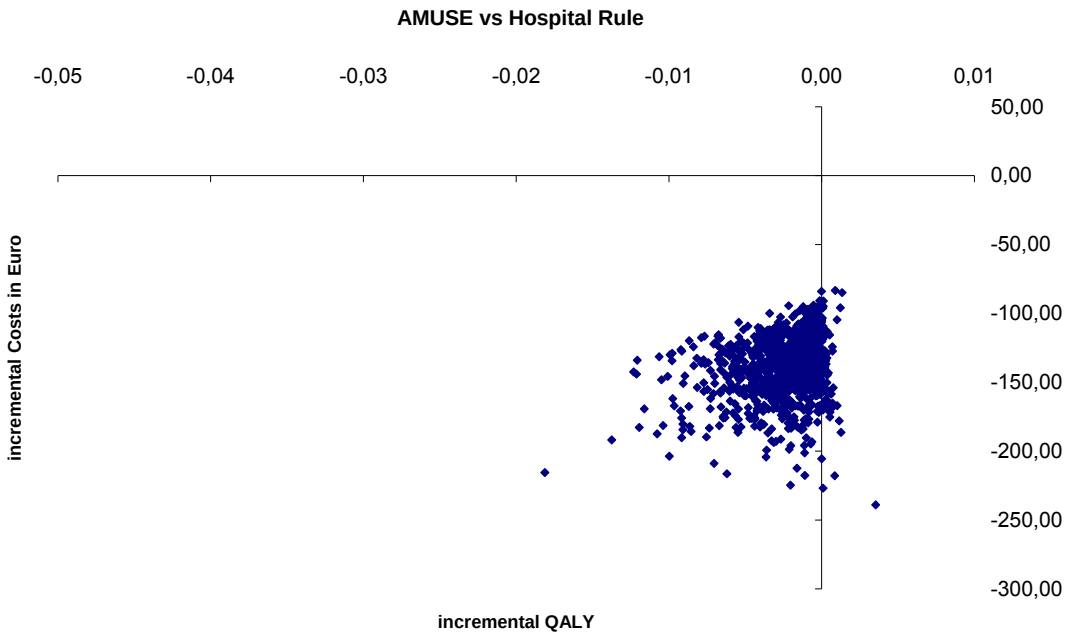
Table 4. *Results of the cost-effectiveness analysis.*

Diagnostic strategy	Life Years	QALYs	Costs
AMUSE	4.8723	3.8532	€ 3,589
Hospital rule	4.8774	3.8557	€ 3,727
Hospital	4.8782	3.8562	€ 3,768
Combination of hospital (50%) and hospital rule (50%)	4.8778	3.8559	€ 3,747

The probabilistic sensitivity analysis showed that the simulation results of the cost and QALY outcomes of the diagnostic strategies were comparable (data not shown). The incremental costs and QALYs from the Monte Carlo simulation comparing the AMUSE strategy and the hospital rule strategy are all in the south of the cost-effectiveness plane, and mostly in the southwest quadrant. This indicates cost savings for (in majority) a QALY loss. The cost-effectiveness acceptability curves show that the hospital strategy has the lowest probability of being cost-effective for a threshold of the iCER up to € 68.000. The AMUSE strategy has the highest probability of being cost-effective as long as society

demands less than € 100.000 compensation for a QALY loss. For a threshold of € 40,000, the probability that the AMUSE strategy is cost-effective is 72%, while for a threshold of € 80,000 it is still 44%.

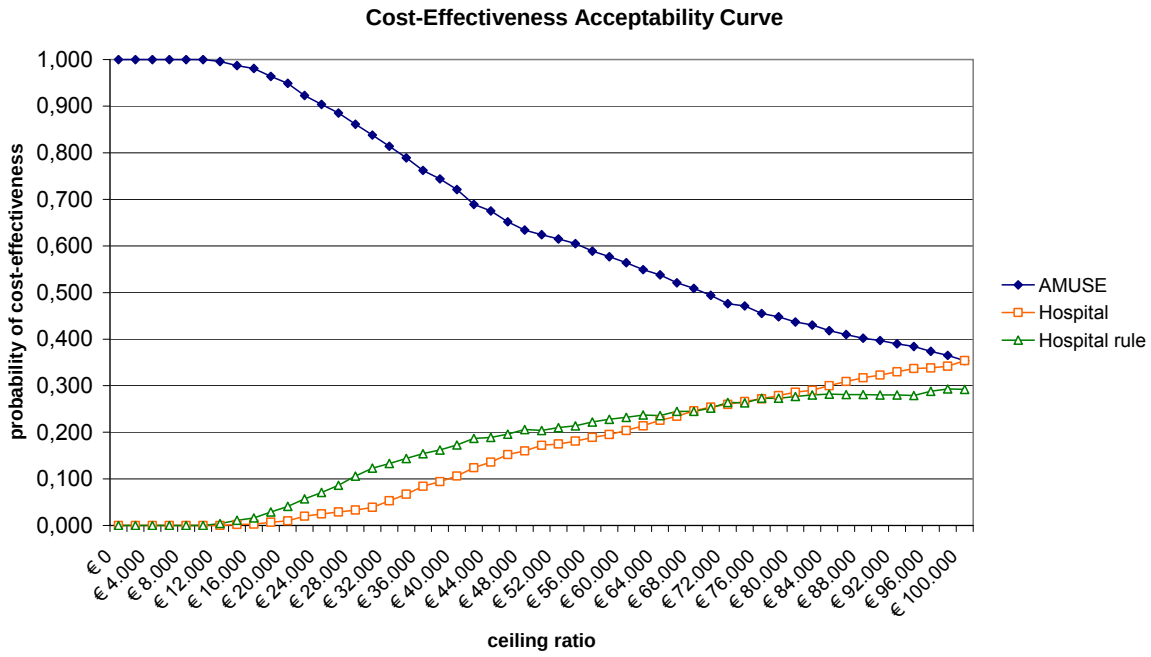
Figure 2. *Cost-effectiveness plane.*



Additional sensitivity analyses

The discounting rate and age did not influence the result. Across a range of 30 to 80 years the iCER of the AMUSE strategy versus the hospital rule strategy varied with only € 1.300 (data not shown). If the sensitivity of the AMUSE strategy was decreased from 0.9265 to 0.9032 the iCER amounted to € 40,000. An increase of the costs of the AMUSE diagnostic strategy of € 27 to € 195 per patient, resulted in an iCER of € 40.000. A wide range of variation in the costs for health states and events did not change our results substantially. The results of the sensitivity analyses are presented in Table 5.

Figure 3. *Cost-effectiveness acceptability curves.*



DISCUSSION

The model based cost-effectiveness analysis showed that the AMUSE strategy, which was deemed to be safe clinically, was associated with a minimal (less than 0.01) loss of QALYs. Also, the cost saving associated with the strategy was relatively small (€ 138). This resulted in a marginally accepTable iCER of the AMUSE strategy versus the next best alternative, the hospital rule strategy (€ 55,753/QALY). However, the cost-effectiveness acceptability curves show that the AMUSE strategy has a higher probability of being cost-effective than the alternatives for thresholds up to € 100.000. For a threshold of € 40,000, the probability that the AMUSE strategy is cost-effective is 72%. Hence, it can be concluded that the AMUSE strategy for the diagnosis of suspected deep vein thrombosis with a point of care d-dimer test combined with a clinical decision rule in primary care is cost-effective.

Some details of our model study require attention. Some costs of health states and events were estimates based on expert opinion or are partially based on assumptions. However, the sensitivity analyses show that for a wide range of

Table 5. *Results of the sensitivity analyses.*

Parameter in the sensitivity analysis	Diagnostic strategy	QALYs	Costs	iCER
Base case	**AMUSE**	**3.8532**	**€ 3,589**	**€ 55,753**
	Hospital rule	**3.8557**	**€ 3,727**	**/QALY**
Undiscounted	AMUSE	3.8820	€ 3,660	€ 56,436
	Hospital rule	3.8845	€ 3,801	/QALY
Sensitivity AMUSE strategy	AMUSE	3.8519	€ 3,574	€ 40,000
0.9032 instead of 0.9265	Hospital rule	3.8557	€ 3,727	/QALY
Costs AMUSE strategy	AMUSE	As in	€ 3,628	€ 40,000
€ 195 instead of € 168	Hospital rule	base case	€ 3,727	/QALY
Costs of PTS high value	AMUSE		€ 9,919	€ 68,767
€ 10,580 instead of € 3,247	Hospital rule	As in	€ 10,089	/QALY
Costs of PTS low value	AMUSE	base case	€ 907	€ 50,240
€ 140 instead of € 3,247	Hospital rule		€ 1,031	/QALY
Costs of CNS bleed high value	AMUSE		€ 3,637	€ 56,706
€ 56,838 instead of € 28,419	Hospital rule	As in	€ 3,777	/QALY
Costs of CNS bleed low value	AMUSE	base case	€ 3,565	€ 55,277
€ 14,210 instead of € 28,419	Hospital rule		€ 3,701	/QALY
Costs of PTS incident high value	AMUSE		€ 4,025	€ 58,972
€ 10,670 instead of € 3,367	Hospital rule	As in	€ 4,171	/QALY
Costs of PTS incident low value	AMUSE	base case	€ 3,404	€ 54,466
€ 274 instead of € 3,367	Hospital rule		€ 3,539	/QALY
Costs of event DVT high value	AMUSE		€ 3,819	€ 60,499
€ 2,644 instead of € 1,322	Hospital rule	As in	€ 3,969	/QALY
Costs of event DVT low value	AMUSE	base case	€ 3,474	€ 53,379
€ 661 instead of € 1,322	Hospital rule		€ 3,606	/QALY
Costs of event PE high value	AMUSE		€ 3,607	€ 51,427
€ 8,420 instead of € 4,210	Hospital rule	As in	€ 3,735	/QALY
Costs of event PE low value	AMUSE	base case	€ 3,580	€ 57,916
€ 2,104 instead of € 4,210	Hospital rule		€ 3,723	/QALY
Costs of event major bleed high value	AMUSE		€ 3,620	€ 56,386
€ 11,497 instead of € 4,211	Hospital rule	As in	€ 3,759	/QALY
Costs of event major bleed low value	AMUSE	base case	€ 3,578	€ 55,534
€ 2,104 instead of € 1,688	Hospital rule		€ 3,716	/QALY
Costs of event CNS bleed high value	AMUSE		€ 3,592	€ 55,810
€ 22,562 instead of € 11,281	Hospital rule	As in	€ 3,730	/QALY
Costs of event CNS bleed low value	AMUSE	base case	€ 3,588	€ 55,725
€ 5,641 instead of € 11,281	Hospital rule		€ 3,725	/QALY

variation in these costs our results do not change substantially. The cost-effectiveness outcome is strongly influenced by the sensitivity of the diagnostic strategies. While the sensitivity of the hospital rule strategy was based on a meta-analysis including over 6000 patients, the estimates for the hospital and AMUSE strategies were based on studies including 1100 and 1000 patients respectively. This resulted in larger uncertainty for the sensitivity of these strategies. In current practice it is likely that hospitals use a mix of the hospital and hospital rule strategy. Therefore, our results can be considered as conservative. Finally, it could be argued that results would be more favourable if a more sensitive d-dimer test combined with the decision rule would have been used in the AMUSE strategy. However, in that case also the specificity is likely to be lower resulting in more patients referred to secondary care, and hence less cost savings.

For clinical practice, implementation of the AMUSE strategy results in the exclusion of DVT in approximately 50% of patients in primary care. This may have the added benefit of convenience for the patients, since referral for ultrasound is not necessary, and may enable the general practitioner to direct attention at finding alternative diagnoses without delay. Although the general practitioner, or the practice assistant, spends extra time to perform the d-dimer test and apply the rule (for which extra costs were included in our model), the prospective study proved that implementation in general practice was highly feasible. In order to facilitate successful implementation a reimbursement for the extra time of the general practitioner would be appropriate.

In summary, the AMUSE strategy to exclude DVT in primary care is not only safe, but also cost-effective as compared to hospital based strategies, with or without a rule, to diagnose DVT.

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APPENDIX

DETAILS OF COST CALCULATIONS (EURO'S, 2004)

A. *Costs of the diagnostic strategies*

Parameter	mean value	Source
Diagnostic strategies		
AMUSE strategy	167,82	
at GP		
GP consultation	20,60	Dutch Cost Manual
# of GP consultations	2,00	AMUSE
Costs of d-dimer	9,25	Company
Costs of performing d-dimer	10,30	Dutch Cost Manual
in hospital		
Costs of blood draw	10,64	Dutch Cost Manual
Costs of a lab procedure	1,78	Dutch Cost Manual
# lab procedures	5,00	Haematology (3), clinical chemistry (2); expert opinion
Costs of 1 ER visit	141,78	Dutch Cost Manual
Costs per ultrasound	40,69	Dutch Cost Manual
# of ultrasounds rule	1,29	Wells, 2003
Hospital strategy	251,08	
# of GP consultations	1,00	assumption
# lab procedures	5,00	Haematology (3), clinical chemistry (2); expert opinion
Costs of 1 ER visit	141,78	Dutch Cost Manual
# of ultrasounds	1,70	Kraaijenhagen, 1997
Hospital rule strategy	226,54	
# of GP consultations	1,00	assumption
Blood draw	10,64	Dutch Cost Manual
# lab procedures & d-dimer	6,00	Haematology (3), clinical chemistry (2), d-dimer; expert opinion.
Costs of 1 ER visit	141,78	Dutch Cost Manual
# of ultrasounds	1,29	Wells, 2003
Travel for diagnosis		
Travel to GP	2,85	
Travel to hospital	7,38	
GP km	1,80	Dutch Cost Manual
hospital km	7,00	Dutch Cost Manual
Costs of km per car	0,16	Dutch Cost Manual
Costs of car parking	2,55	Dutch Cost Manual
GP % by car	0,50	AMUSE, se 0,02, beta distribution
Hospital % by car	1,00	AMUSE

GP: General Practitioner

***B**. Costs associated with events*

Parameter	Mean value	se	Distribution	Source
Event DVT	1322,45			
GP consultation	29,60			Dutch Cost Manual
# of GP consultations	0,83	0,30	gamma	AMUSE
Home care compression therapy	480,62			AMUSE, Dutch Cost Manual
LMWH 7 days	66,68			Pharmacotherapeutic Compass
Coumarins 6 months	85,61			Pharmacotherapeutic Compass
specialist visit	57,12			Dutch Cost Manual
# control visits specialist	2,79	0,84	gamma	AMUSE
INR control visit	8,46			Thrombosis Service
# INR control visits	16,38	1,28	gamma	AMUSE
compression stockings	60,38			Health care insurance company
Hospital day	485,52			Dutch cost manual
# hospital days	0,63	0,11	gamma	AMUSE
Event PE	4209,77			
GP consultation	29,60			Dutch Cost Manual
# of GP consultations	1,42	1,07	gamma	AMUSE
ER visit	141,78			Dutch Cost Manual
CT thorax	132,35			Dutch Cost Manual
ECG	25,41			Dutch Cost Manual
Blood draw	10,64			Dutch Cost Manual
Lab procedures	1,78			Dutch Cost Manual
# lab procedures	5,00			Haematology (3), clinical chemistry (2); expert opinion
Hospital day	485,52			Dutch Cost Manual
# hospital days	7,00			Expert opinion
LMWH 7 days	66,68			Pharmacotherapeutic Compass
Coumarins 6 months	85,61			Pharmacotherapeutic Compass
# control visits specialist	2,79	0,84	gamma	AMUSE
# INR control visits	16,38	1,28	gamma	AMUSE

DVT: deep venous thrombosis; PE: Pulmonary emboli

C. Incidence and health state costs associated with Post Thrombotic Syndrome

Parameters [29]	Proportion of patients	Number	Unit costs	source	Costs
Mild to moderate first 6 months					
Specialist contact	1	2,00	€ 57,12	Dutch Cost Manual	€ 114,24
Duplex	1	1,00	€ 90,11	Dutch Cost Manual	€ 90,11
Stockings	1	1,00	€ 60,38	Insurance Company	€ 60,38
Vein ligation and stripping	0,015	1,00	€ 609,90	Dutch Cost Manual	€ 9,15
				Total	273,87
Mild to moderate after 6 months					
Specialist contact	1	2,00	€ 57,12	Dutch Cost Manual	€ 57,12
Duplex	0,25	1,00	€ 90,11	Dutch Cost Manual	€ 22,53
Stockings	1	1,00	€ 60,38	Insurance Company	€ 60,38
				Total	140,02
Severe first 6 months					
Specialist contact	1	2,00	€ 57,12	Dutch Cost Manual	€ 114,24
Duplex	1	1,00	€ 609,90	Dutch Cost Manual	€ 90,11
Pneumatic compressor	0,07	1,00	€ 61,01	Dutch Cost Manual	€ 4,27
Stockings	1	1,00	€ 60,38	Insurance Company	€ 60,38
Steroid creams (locoid crème)	0,1		€ 9,92		€ 0,99
Antibiotic (ciprofloxacine, 10 days bid)	0,75		€ 32,99		€ 24,74
Hospital days for ulcers	0,15	14,5	€ 485,52	Dutch Cost Manual	€ 1.056,01
Home care for ulcers	0,85	182,5	€ 60,08	Dutch Cost Manual	€ 9.319,60
				Total	€ 10.670,34
Severe after 6 months					
Specialist contact	1	2,00	€ 57,12	Dutch Cost Manual	€ 114,24
Pneumatic compressor	0,07	1,00	€ 61,01	Dutch Cost Manual	€ 4,27
Stockings	1	1,00	€ 60,38	Insurance Company	€ 60,38
Steroid creams (locoid crème)	0,1		€ 9,92	Pharmacotherapeutic Compass	€ 0,99
Antibiotic (ciprofloxacine, 10 days bid)	0,75		€ 32,99	Pharmacotherapeutic Compass	€ 24,74
Hospital days for ulcers	0,15	14,5	€ 485,52	Dutch Cost Manual	€ 1.056,01
Home care for ulcers	0,85	182,5	€ 60,08	Dutch Cost Manual	€ 9.319,60
				Total	€ 10.580,23
Weigthed average moderate and severe first 6 months (costs of incident)					
moderate	0,70	€ 273,87			€ 191,71
severe	0,30	€ 10.670,34			€ 3.175,69
					€ 3.367,41
Weigthed average moderate and severe after 6 months (costs of health state)					
moderate	0,70	€ 140,02			€ 98,02
severe	0,30	€ 10.580,23			€ 3.148,88
					€ 3.246,89

D. *Costs associated with event major (gastro intestinal) VKA bleed*

Major bleed tractus digestives	Expert 1 hematologist		Expert 2 hematologist		Expert 3 vascular internist		Expert 4 gastroenterologist	
	min	max	min	max	min	max	min	max
Days of hospital admission #	3	21	2	2	3	10	4	10
	€ 1.456,56	€ 10.195,92	€ 971,04	€ 971,04	€ 1.456,56	€ 4.855,20	€ 1.942,08	€ 4.855,20
mean all experts	*€ 3.337,95*							
max all experts	*€ 10.195,92*							
min all experts	*€ 971,04*							
Diagnostic imaging								
Gastroscopy #	1	2	1	1	1	2	2	3
	€ 144,50	€ 289,01	€ 144,50	€ 144,50	€ 144,50	€ 289,01	€ 289,01	€ 433,51
mean all experts	*€ 234,82*							
max all experts	*€ 433,51*							
min all experts	*€ 144,50*							
CT scan #	0	0	1	1	0	0	0	0
	€ 0,00	€ 0,00	€ 132,35	€ 132,35	€ 0,00	€ 0,00	€ 0,00	€ 0,00
mean all experts	*€ 33,09*							
max all experts	*€ 132,35*							
min all experts	*€ 0,00*							
Lab tests #	3	20	2	2	3	5	2	8
	€ 37,29	€ 188,30	€ 28,41	€ 28,41	€ 37,29	€ 55,06	€ 28,41	€ 81,71
mean all experts	*€ 60,61*							
max all experts	*€ 188,30*							
min all experts	*€ 28,41*							
Medication								
Vitamin K (konakion)	1		1				1	3
one dose	€ 1,02		€ 1,02				€ 1,02	€ 3,06
mean all experts	*€ 1,53*							
max all experts	*€ 3,06*							
min all experts	*€ 1,02*							
Proton pump inhibitor (omeprazol)	1				1		1	
6 months	€ 226,20				€ 226,20		€ 226,20	
mean all experts	*€ 226,20*							
max all experts	*€ 226,20*							
min all experts	*€ 226,20*							
Care after hospital admission								
INR control visit	x		x				x	
24 visits	€ 202,98							
Mean all experts	*€ 202,98*							
outpatient clinic	x		x		x		x	
2 visits	€ 114,24							
Mean all experts	*€ 114,24*							
Mean sumscore		€ 4.211,41						
Max sumscore		€ 11.496,56						
Min sumscore		€ 1.688,39						

Chapter 7

COMMON ALTERNATIVE DIAGNOSES AFTER EXCLUSION OF DEEP VENOUS THROMBOSIS IN SYMPTOMATIC PATIENTS IN GENERAL PRACTICE

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Submitted

ABSTRACT

Purpose: To assess the frequency and the management of alternative diagnoses in association with clinical symptoms, risk factors for thrombosis and strategy outcomes in patients after exclusion of deep vein thrombosis (DVT) in general practice.

Methods: A sub-study to a management study in primary care in the Netherlands involving 1028 consecutive patients with complaints suspect for DVT (AMUSE). Data were recorded by general practitioners after one week and extracted from a three month follow-up questionnaire for patients.

Results: The most frequent diagnoses were; muscle rupture (18.5%), chronic venous insufficiency (CVI) (14.6%), erysipelas/cellulitis (12.6%) and superficial thrombophlebitis (SVT) (10.9%). Swelling (OR 8.6) and redness (OR 21.3) were strongly associated with erysipelas. Absence of swelling (OR 0.6), redness (OR 0.6), age >70 (OR 0.4) and absence of leg trauma (OR 0.5) were associated with muscle rupture/ hematoma. Painful palpation of the vein had a strong association with SVT (OR 3.7). A non acute onset (OR 0.5), age >70 (OR 2) and malignancies active and not active (OR 2.4-2.1) were associated with CVI. A low score on the AMUSE strategy (clinical decision rule to safely exclude DVT) was associated with muscle rupture/hematoma (OR 3.6). An expectative policy was used in one third of patients, less often in erysipelas (OR 0.2) and frequently in CVI (OR 2.4).

Conclusions: Common alternative diagnoses in primary care are muscle rupture, CVI, erysipelas/cellulitis and SVT. Alternative diagnoses have strong association with the clinical presentation. An expectative policy was sufficient in one third of patients.

INTRODUCTION

The timely diagnosis of deep vein thrombosis (DVT) is of critical importance since a missed diagnosis can result in a potentially fatal pulmonary embolism. [1] The clinical symptoms of DVT, however, are not sufficiently specific to allow for a prompt diagnosis based on clinical assessment alone. Unilateral complaints of painful swelling of the leg, with or without accompanying redness are common symptoms of many other conditions. This may explain that only about 15% of patients who are evaluated by ultrasound examination do actually have DVT. [2, 3, 4] The majority of patients initially suspected of DVT are eventually assigned an alternative diagnosis. Objective testing – notably repeated compression B-mode ultrasound of the legs - can be, and is currently, avoided in over 30% of patients presenting with complaints suspected of DVT using a clinical decision rule in combination with d-dimer assay. [3] It has been suggested that this reduction of the number of unnecessary ultrasound examinations is undesirable since these examinations could be helpful in establishing alternative diagnoses in case of absence of DVT. [5]

In one study in secondary care patients suspected of DVT it was found that an alternative diagnosis was reached in only 48% of the patients and no diagnosis was obtained in 52% of patients. [5] We explored the clinical diagnosis and management of patients presenting in primary care with complaints of unilateral swelling of the leg. In a descriptive analysis we addressed the following questions: What are the most common diagnoses in these patients? Can these alternative diagnoses be characterized by specific signs or symptoms? How are risk factors for thrombosis distributed in alternative diagnoses? What are the results of the clinical decision rule to exclude DVT in these alternative diagnoses? What treatment strategies are adopted and finally, what happens to these patients in a three month follow up period?

METHODS

A management study was conducted in primary care in the Netherlands from March 2005-January 2007 involving 1028 consecutive patients who presented with complaints suspect for DVT. This study was conducted in three regions of

the Netherlands and was named: the Amsterdam Maastricht Utrecht Study on venous thrombo-Embolism (AMUSE). [7]
In AMUSE, the safety and efficiency of using a previously published clinical decision rule in combination with a point of care D-dimer assay (Clearview Simplify D-dimer assay, Inverness Medical, Bedford, UK) to exclude deep vein thrombosis in primary care was evaluated.[8] Patients with a score ≤ 3 were not referred for ultrasound and received care as usual. They were instructed to contact the general practitioner in case symptoms worsened. Patients with a score ≥ 4 were referred for ultrasound and subsequently treated according to their diagnosis. In case of thrombosis they received anticoagulant therapy. Patients without thrombosis received care as usual. All patients were subsequently evaluated at day 7 ± 2 by their general practitioner. This procedure is here further referred to as AMUSE strategy.

Variables

At presentation and at the second visit after one week, the general practitioner filled out a systematic Case Record Form (CRF). The following items were recorded: leg complaints, onset of complaints, medical history, risk factors for venous thrombosis, medication use, findings at physical examination, ultrasound result (if ultrasound was conducted), result of decision rule, most likely diagnosis (working diagnosis) and installed therapy. The clinical decision rule used the following dichotomous variables: male gender, use of hormonal contraceptives, active malignancy in the past 6 months, recent surgery in the previous month, absence of leg trauma, distension of collateral veins, difference in calf circumference≥3 cm, and D-dimer (Simplify®) abnormal.

Patients

Of the 1028 patients included 138 were documented to have thrombotic disease. At the one week follow-up visit 127 patients were diagnosed with DVT and as a consequence anticoagulant treatment was installed. Venous thromboembolism furthermore occurred in eleven patients that were initially not diagnosed with DVT (1.1%). The remainder of patients however did not experience important health problems in the course of a three month follow up period. All patients

received a questionnaire three months after inclusion. This questionnaire comprised questions on complaints, visits to the general practitioner and specialists for leg problems, and questions on installed therapy for these problems (if applicable).

Alternative diagnoses

For the current study we analyzed the prevalence of the alternative diagnoses in our patient population, as recorded by the general practitioners during the follow-up contact, thus after results of the ultrasound were known for referred patients (score ≥4). The general practitioner could choose from a list of ten possible alternative diagnoses to be recorded on the CRF: deep vein thrombosis (DVT), erysipelas/cellulitis, chronic venous insufficiency (CVI), lymph edema, superficial thrombophlebitis (SVT), mycosis, muscle rupture/hematoma, Baker's (popliteal) cyst, ankle arthritis and pelvic tumor. They were asked to record the most likely diagnosis. In case this diagnosis was not among these ten pre-specified diagnoses, they could record their diagnosis as open text.

Statistical analysis

We first assessed the frequency of DVT and all alternative diagnoses in our study population. Then, for the four most prevalent alternative (i.e. non-DVT) diagnoses separately, the presence of signs and symptoms was described and the association of signs and symptoms with each diagnosis was estimated using the Chi-square test for categorical variables. Similarly, known risk factors for thrombosis, results of the clinical decision rule, therapeutic strategies and referral and follow-up practices were analyzed for their respective association with each alternative diagnosis. Furthermore Odds Ratio's and their 95% confidence intervals were calculated comparing the persons with a specific diagnosis (DVT, muscle rupture/hematoma, CVI, erysipelas/cellulitis) to those without a specific diagnosis (SPSS 13.0 for Windows). A p-value ≤ 0.05 was considered significant.

RESULTS

At the one week follow-up visit, 669 CRF's (65.1%) contained a specified diagnosis; Besides DVT, the four most prevalent alternative diagnoses were muscle rupture/hematoma (18.5%), CVI (14.6%), erysipelas/cellulitis (12.6%), and SVT≤ (10.9%). The other alternative diagnoses mentioned were each present in less than 6 %.(lymph edema (5.5%), Baker's (popliteal) cyst (4.5%), pelvic tumor (0.6%), ankle arthritis (1.8%), mycosis (0%)). Fifteen percent of the general practitioners described an alternative diagnosis other than the ten diagnostic options mentioned in the CRF. The added alternatives by general practitioners were mainly described as: muscle complaints, lower back hernia, known edema and gonarthrosis.

Muscle rupture/hematoma was the only diagnosis that was seen equally frequent in men and women; other alternative diagnoses concerned significantly more often women ($p \leq 0.05$). The alternative diagnoses erysipelas, CVI and SVT were seen as often in patients that underwent ultrasound examination as in patients that were not assessed by ultrasound; only in the group of patients diagnosed as muscle rupture/hematoma significantly less ultrasound examinations were done.

Association with signs and symptoms

Table 1 shows the distribution of signs and symptoms for each of the four most frequent alternative diagnoses separately.

'Pain' as well as 'swelling' were common findings in the four most frequent alternative diagnoses as well as in DVT. Painful palpation of the venous traject however was observed to be discriminatory for SVT. Compared to the other alternative diagnoses, CVI presented more often with swelling of the entire leg.

We observed that 'redness' is the most distinctive features of erysipelas and is present in 91% of these patients. This symptom on the other hand is more often found to be absent in muscle rupture/hematoma. For most of the alternative diagnoses, in slightly more than half of the cases, the onset of complaints was acute (similar to patients diagnosed with DVT) an exception was formed by the non acute onset of CVI in a majority (61.8%) of cases.

Table 1. Signs and symptoms for each alternative diagnosis besides DVT.

DISEASE	Erysipelas/cellulitis N=84		Muscle rupture/hematoma N=124		CVI N=98		SVT N=73		DVT N=138	
	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)
SIGNS, SYMPTOMS										
Right side	38(49)		56(49)		48(53)		49		56(42)	
Pain	76(92)		113(92)	< 0.05 OR=2.1 (1.04-4.03)	71(76)	<0.01 OR=0.4 (0.25-0.7)	69(95)	<0.05 OR=3.1 (1.1-8.3)	118(86)	
Swelling	80(96)	<0.001 OR=8.6 (2.8-26.1)	86(69)	<0.01 OR=0.6 (0.36-0.86)	80(84)		51(70)		126(91)	<0.001 OR=3.4 (1.9-6.2)
Swelling entire leg	15(19)		18(15)	<0.05 OR=0.2 (0.09-0.29)	30(32)	0.01 OR=1.9 (1.2-3.03)	9(13)	0.05 OR=0.5 (0.24-1.0)	48(35)	<0.001 OR=2.1 (1.5-3.2)
Painful palpation vein	39(48)		67(57)		49(47)		57(80)	<0.001 OR=3.7 (2.0-6.7)	69(53)	
Redness	76(91)	<0.001 OR=21.3 (10.2-44.3)	15(12)	<0.001 OR=0.6 (0.34-0.99)	30(33)		37(51)	<0.05 OR=1.8 (1.1-2.8)	53(40)	
Collateral vein dilatation	10(26)		11(9)		20 (21)		19(26)		29(21)	<0.05 OR=1.7 (1.1-2.6)
Acute onset	48(61)		71(59)		34(38)	<0.01 OR=0.5 (0.34-0.86)	40(56)		76(57)	

P values concern the comparison of patients with single diagnosis present versus all other patients (diagnosis absent) and are only presented if <0.05. Then, odds ratios and 95% confidence intervals are included as well.

Table 2. Risk factors for each alternative diagnosis besides DVT.

DISEASE	Erysipelas/cellulitis N=84		Muscle rupture/hematoma N=124		CVI N=98		SVT N=73		DVT N=138	
	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)	N (%)	P OR (95% CI)
RISK FACTORS										
Malignancy active	2(2)		2(2)	<0.05 OR=0.25 (0.1-0.9)	10(10)	<0.05 OR=2.4 (1.6-3.8)	4(6)		15(11)	<0.01 OR=2.6 (1.4-4.9)
Malignancy not active	4(5)		4(3)		10(10)	<0.05 OR=2.1 (1.0-4.4)	5(7)		14(10)	<0.05 OR=1.9 (1.0-3.4)
Age > 70 yr	28(35)		22(19)	0.001 OR=0.4 (0.27-0.7)	42(44)	<0.01 OR=2 (1.3-3.1)	27(38)		39(29)	
Previous DVT	5(7)	<0.05 OR=0.3 (0.1-0.8)	13(15)		19 (20)		22(31)	0.001 OR=2.9 (1.7-5.1)	30(22)	<0.05 OR=1.6 (1.1-2.6)
Previous SVT	8(10)		4(3)	< 0.05 OR=0.3 (0.12-0.8)	7(7)		19(26)	<0.001 OR=5.2 (2.8-9.5)	9(7)	
Recent surgery	3(4)		4(3)	<0.05 OR=0.4 (0.1-0.98)	11(11)		3(4)		11(8)	
Travel	6(8)		13(11)		7(7)		8(11)		20(15)	<0.05 OR=1.9 (1.1-3.3)
Trauma absent	59(70)		77(62)	<0.01 OR=0.5 (0.34-0.8)	77(79)		58(79)		109(79)	
Male gender	37(44)		56(45)		30(31)	<0.05 OR=0.7 (0.4-1.1)	19(26)	<0.05 OR=0.5 (0.3-0.9)	69(50)	<0.001 OR=1.9 (1.3-2.7)
Varicositas	24(29)		27(22)	<0.001 OR=0.4 (0.27-0.7)	51(55)	<0.001 OR=2.4 (1.6-3.8)	47(67)	<0.001 OR=4.2 (2.5-7.1)	44(33)	

P values concern the comparison of patients with single diagnosis present versus all other patients (diagnosis absent) and are only presented if <0.05. Then, odds ratios and 95% confidence intervals are included as well

Association with risk factors for thrombosis

The distribution of classic risk factors for venous thromboembolism for the four alternative working diagnoses separately was compared to the distribution of these risk factors in patients diagnosed with DVT. (Table 2)

Malignancies, active or not active, were seen as often in patients with CVI as in patients with DVT, but is less frequent in patients diagnosed with SVT.
Patients with CVI were more frequently old (>70 year) while patients with muscle rupture/ hematoma were more often younger. For DVT the majority of patients were younger than 70 years (72%).
SVT was more frequent among those with a history of DVT and in patients with previous SVT. Varicositas was more frequent in SVT and in CVI but less often observed in muscle rupture/hematoma. For all the alternative diagnostic options studied, surgery and travel were not obvious risk indicators. Many risk factors for thrombosis were negatively associated with "muscle rupture/hematoma".

Association with strategy outcomes

We analyzed the outcomes of the AMUSE strategy for the four alternative diagnoses and compared the outcomes to the strategy outcomes of patients with DVT. (Table 3)

For Erysipelas/cellulitis, CVI and SVT in approximately half of the cases a non-low result on the strategy was found (score of ≥ 4). This was mainly due to a positive result on the D-dimer assay. This is in contrast to the findings for the diagnosis muscle rupture/hematoma where the D-dimer assay was found to be negative in 74% of patients. A non-low risk based solely on a high clinical score was rare and relatively more often, but not significantly, found in erysipelas (8.3%). In DVT, as could be expected, a non-low score on the strategy was most frequent (93%). Although the clinical score was ≥4 in 41% of patients; a non-low score here also was mainly due to a positive D-dimer assay.

Table 3. *Result of the clinical decision rule for each alternative diagnosis besides DVT, divided by result of D-dimer test (DD) and clinical items (CL)*

DISEASE		Erysipelas/cellulitis N=84	Muscle rupture/hematoma N=124	CVI N=98	SVT N=73	DVT N=138
		P	P OR (95% CI)	P	P OR (95% CI)	P OR (95% CI)
RESULT CLINICAL DECISION RULE						
Low score *(≤ 3)*	*DD- CL-*	**37(44%)**	**92 (74%)** <0.001 OR=3.6 (2.4-5.6)	**50 (51%)**	**30 (41%)**	**9 (6%)** <0.001 OR=0.05 0.02-0.09)
Non-low score *(≥ 4)*	*DD- CL+*	7 (8.3%)	4 (3.3%)	3 (3%)	3 (4%)	13 (10%) <0.05 OR= 2.4 (1.2-4.5)
	DD+ CL-	31 (37%)	24 (19%) <0.001 OR=0.4(0.25-0.64)	38 (39%)	35 (48%) <0.05 OR=2.0 (1.2-3.3)	76 (59%) <0.001 OR=2.7 (1.9-3.9)
	DD+ CL+	7 (8.3%)	3 (2.4%) <0.01 OR=0.2 (0.07-0.61)	6 (6%)	3 (4%)	39 (31%) <0.001 OR=6.1(3.9-9.7)
Total non-low score		**45 (54%)**	**31 (25%)**	**47 (48%)**	**41 (56%)**	**128 (93%)**

P values concern the comparison of patients with single diagnosis present versus all other patients (diagnosis absent) and are only presented if <0.05. Then, odds ratios and 95% confidence intervals are included as well (D-dimer test result was missing in approximately 2% of patients)

Table 4. Installed therapy for each alternative diagnosis

DISEASE	Erysipelas/cellulitis N=84		Muscle rupture/hematoma N=124		CVI N=98		SVT N=73	
	N(%)	P OR (95% ci)	N(%)	P OR (95% ci)	N(%)	P OR (95% ci)	N(%)	P OR (95% ci)
TREATMENT								
Antibiotics	59(70)	<0.001 OR=78.9 (40.4-153.8)	2(2)	<0.001 OR=0.1(0.03-0.4)	3(3)	<0.01 OR=0.2 (0.07-0.66)	4(6)	
LMWH	3(3.6)	<0.01 OR=0.2 (0.07-0.7)	0 (0)		1(1)	<0.001 OR=0.06 (0.01-0.32)	9(12)	
Coumarins	0(0)		0(0)		0(0)		5(7)	
NSAID	5(6)		15(12)		7(7)		4(19)	<0.05 OR=2.4 (1.28-4.61)
Diuretics	4(5)		0(0)		10(10)	<0.001 OR=5.8 (2.4-13.7)	0(0)	
Compression therapy	29(35)		14(11)	<0.001 OR= 0.25 (0.14-0.44)	32(33)		29(40)	
Physiotherapy	0(0)		19(15)	<0.001 OR=6.9 (3.4-13.95)	3(3)		0(0)	
Expectative	6(7)	<0.001 OR=0.2 (0.08-0.4)	51(41)	<0.001 OR=2.4 (1.6-3.6)	31(32)		20(27)	

P values concern the comparison of patients with single diagnosis present versus all other patients (diagnosis absent) and are only presented if <0.05 (except for frequency = 0)

Therapeutic strategies

The installed therapy as recorded in the CRF at week 1 was analyzed for the four most prevalent alternative diagnoses. The possible therapeutic options were: antibiotic therapy, pain reduction (NSAID), antithrombotic therapy (LMWH and coumarins), compression therapy, physiotherapy or no therapy (expectative). (Table 4)

In almost 30% of cases the policy was expectative and no therapy was installed (27-41%). For the diagnosis muscle rupture/hematoma an expectative policy was significantly more often followed. In contrast, for the diagnosis erysipelas/cellulitis only in 7 % of cases no immediate action was undertaken; in 70 % of cases antibiotic therapy was installed, this was in 35 % combined with compression therapy.

For CVI, when therapy was installed, compression therapy was the most popular form of therapy (33 %) and furthermore diuretics (10 %) as well as NSAID's (7 %) were prescribed. In the treatment of SVT compression therapy also was the main therapeutic feature (40 %). The four additional forms of therapy were antibiotics, NSAID, LMWH and coumarins (6 %, 19%, 12% and 7% respectively). In almost 30% no therapy was given.

Referral and follow-up

The remainder of patients was followed up in general practice. Patients were referred for further evaluation and therapy to specialists in secondary care in 15-20% of cases. Patients with the working diagnosis muscle rupture/hematoma and CVI were referred, in respectively 10% and 9%, to the surgery department for evaluation. Patients with the working diagnosis SVT and erysipelas were most commonly referred to a dermatologist (9-11%).

The majority of patients visited their general practitioner in the follow up of leg complaints over the course of three months two to three times (mean 2.41, SD 3.7).

For most alternative diagnoses the maximum number of visits lies between 5-6.

In the follow-up period of three months eleven of the patients (1.1%) that were not diagnosed with DVT at presentation (7 in the low score group, 4 in the non-

low score group) were diagnosed with venous thromboembolic disease, one of which was fatal. Two of these 11 patients were diagnosed with DVT within two days after presentation; the alternative diagnoses of the other 9 patients were SVT (3), muscle rupture (1), lymph edema (1) and other (1). For 3 patients, 2 in the low score group and one in the non-low score group, no alternative diagnosis was stated, these patients were eventually diagnosed with pulmonary embolism.

DISCUSSION

Alternative diagnoses in the differential diagnosis of DVT

In our primary care population muscle rupture/ hematoma, erysipelas/cellulitis, CVI and SVT were the most prevalent alternative diagnoses in patients, initially suspected of having DVT. No specific diagnosis was made in 35% of the patients. Alternative diagnoses in patients suspected of DVT in primary care differ essentially from alternative diagnoses in secondary care, which are mainly based on ultrasound findings. A study performed in secondary care reported as the most prevalent alternative diagnoses in secondary care: venous disease, edema of other origin and osteo arthrosis of the knee. No diagnosis was made in 33% of patients. [5] In the hospital setting ultrasound examination contributed to the alternative diagnoses in 36 % of cases, and was thought to be useful in 81%. The avoidance of ultrasound examinations in 50% of patients suspected of DVT in primary care however did not have an impact on the prevalence of alternative diagnoses. The same distribution of alternative diagnoses was found in the group of patients with and without ultrasound performed. This finding suggests that no significant additional information was retrieved from ultrasound examination.

Signs and symptoms, risk factors for thrombosis and D-dimer test result

In addition to physical examination both risk stratification and a diagnostic strategy can provide additional information for the determination of alternative diagnoses; most diagnoses however are made based on combinations of clinical signs. In case of muscle rupture/hematoma, young age, the absence of (entire

leg) swelling or redness, the absence of many risk indicators for thrombosis, and a negative D-dimer assay result were associated with this diagnosis.
For the diagnosis CVI, female gender, a non acute onset, presence of varicositas or swelling of an entire leg, absence of pain and age over 70 years, were the most relevant diagnostic variables. Common features of CVI such as itching, brown hemosiderin skin dispositions, white scar tissue and lipodermatosclerosis were not considered in the list of complaints in the CRF, but will most likely have contributed to the diagnosis. [9] For SVT redness, swelling and painful palpation of the vein were important findings on physical examination, varicositas, previous SVT or DVT and a positive d-dimer test increased the probability of SVT. Finally, erysipelas/cellulitis was characterized by redness and swelling of the leg, and the absence of previous DVT.

Therapeutic strategies and follow-up

An expectative policy in the primary care setting was sufficient for one third of the patients in our cohort. Of patients that were diagnosed with DVT during the follow-up period of 3 months, three out of six had SVT as a working diagnosis and of the patients diagnosed with pulmonary embolism during the 3 month follow-up period no alternative diagnosis was stated. Although the analyses were not pre-specified it is statistically unusual (p=0.026) that of the 9 missed DVT's, 3 occurred in the patients with the working diagnosis SVT. Neither of these patients was treated with anticoagulant medication. This may suggest that patients with thrombosis related afflictions such as SVT as well as patients with essentially non specific complaints require closer surveillance. SVT has been reported in association with DVT in several instances, it is however still unclear how prevalent this event is. [10, 11] Conservative management of SVT mainly focused on pain reduction may therefore be considered to be insufficient.

Limitations of the study

Some limitations of this study have to be mentioned. Firstly, only in 65% of cases a specified diagnosis was given at week one. It is likely that in cases where DVT was confirmed an alternative diagnosis was less often given at week one.

Secondly, the list of alternative diagnoses was limited to ten pre- specified alternative diagnoses and one optional diagnosis. Moreover, limited symptoms for the assessment of the alternative diagnosis were mentioned in the CRF.
It is most likely that patients with a milder presentation of alternative diseases were included in our cohort. When patients present with typical symptoms of fever, shivering and redness and swelling of a sharply demarcated skin area they are most likely not suspected of DVT, but diagnosed as having erysipelas and be treated without delay with antibiotics and compression therapy.
Finally, all alternative diagnoses in our cohort were working diagnoses; no objective diagnostic testing had to be performed to confirm these diagnoses.

CONCLUSIONS

The alternative diagnoses in patients suspected of DVT in primary care were muscle rupture/hematoma, erysipelas/cellulitis, CVI and SVT. These diagnoses differ from alternative diagnoses in secondary care. The avoidance of ultrasound examinations in 50% of patients suspected of DVT in primary care has no impact on the frequency of alternative diagnoses. Alternative diagnoses in primary care can to a certain extent be characterized by the presence or absence of signs and symptoms, risk factors for thrombosis or results on a D-dimer test. An expectative policy in the primary care setting was sufficient for almost one third of patients that were managed in the context of an alternative diagnosis. However, in case of the alternative diagnosis SVT patients may require closer surveillance, since we found that DVT was more prevalent in these patients in our cohort.

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Chapter 8

APPROPRIATE LEVEL AND LENGTH OF POST-THROMBOTIC WARFARIN TREATMENT; AN EVALUATION OF RECENT DEVELOPMENTS

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ABSTRACT

Current treatment and secondary prophylaxis of venous thromboembolism has two major drawbacks. During vitamin K antagonist therapy patients need to be monitored closely to maintain efficacy and minimize the bleeding risk due to fluctuations of the prothrombin time
(INR) and after cessation of therapy there is the problem of recurrent thrombosis, i.e. the catch-up phenomenon.

Recent studies indicate that for most patients vitamin K antagonist therapy aimed at an INR of 2.0 to 3.0 is optimal. For patients with thrombosis due to a temporary risk factor extending treatment beyond 3 months is not needed, while for other patients a minimal duration of one year can be advocated. For patients with cancer, it is beneficial to postpone therapy with vitamin K antagonist and prolong initial LMWH therapy for 3 to 6 months.

New developments are aimed at further individualization of the duration of treatment and at the introduction of agents that are suiTable for long term treatment and do not require monitoring.

INTRODUCTION

For over 50 years vitamin K antagonists, such as warfarin, have been used in the treatment of venous thromboembolism (VTE). [1] Although effective for most patients this therapy is less effective and associated with an increased risk of recurrence during treatment for patients with underlying cancer. [2] Vitamin K antagonists have a slow onset of activity and must be monitored regularly so that the dose can be adjusted to ensure that the protective effect is combined with an accepTable risk of bleeding. Monitoring is done by the determination of the prothrombin time, which is converted into the international normalized ratio (INR). Effective therapy for VTE is reflected by an INR of 2.0-3.0, whereas an INR >3 results in more bleeding without any benefit in the prevention of recurrent thrombotic episodes. [3, 4] The effort of routine coagulation monitoring is costly, makes patient care complex and is a considerable burden on the patients' life during long term therapy.

Present long-term therapy recommendations by the American College of Chest Physicians (ACCP) are that patients with reversible or time-limited factors should be treated for at least 3 months, patients with symptomatic isolated calf vein thrombosis for at least 6-12 weeks [5] and patients with a first episode of VTE without a known risk factor (idiopathic VTE) for at least 6 months. Finally, in patients with recurrent idiopathic VTE or continuing risk factors such as cancer, antithrombin-deficiency, or anti-pospholipid antibody syndrome (APA), treatment for 12 months or longer is recommended. [6]

After cessation of anticoagulant therapy the risk of recurrence is 3% per year in patients with a first episode of VTE associated with a transient risk factor. [7] This risk is much higher, at least 10% per year, in patients without reversible risk factors, including those with prothrombotic abnormalities such as APA and a homozygous factor V Leiden mutation, as well as in patients with cancer. [8] The risk of recurrence is the same for patients with proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) , but the risk of fatal PE is 2-3 fold higher after a previous episode of PE. [9] Residual thrombosis also poses an important independent risk factor for recurrence. [10]

The problem of recurrent thrombosis after cessation of therapy, the continued bleeding risk with longer duration of therapy and the difference in incidence of

recurrence between certain patient groups has led to recent studies on proper duration and intensity of anticoagulant therapy and individualisation of the duration of therapy with vitamin K antagonists. At the same time the development of safe and effective anticoagulants that potentially can replace vitamin K antagonists, but do not need monitoring, is taking place.

RECENT STUDIES ON DURATION

In principle, the duration of anticoagulation for secondary prophylaxis of VTE depends on weighing the efficacy in the prevention of recurrence against the risk of bleeding associated with treatment. The strongest known predictor of recurrence is the presence or absence of a major reversible risk factor.[11-15] When the risk of recurrence is lower the duration of therapy can be shorter whereas for some patients the risk of recurrent VTE may be considered high enough to justify long-term therapy. Kearon et al [16] investigated the possible benefit of long-term treatment for persons with idiopathic thrombosis. After the initial three months of warfarin therapy a prolongation of this regimen for 24 months, aimed at an INR of 2.0 to 3.0, was compared with placebo therapy. Extended warfarin therapy proved to be effective and resulted in a 95 % (95% CI, 63 to 99) reduction of the risk of recurrence, i.e. from 27.4% per patient year in the placebo group to 1.3% per patient year in the group receiving warfarin. This effect was counterbalanced by a risk of major bleeding of 3.8% per person year in the warfarin group versus 0% per person year in the placebo group.

Agnelli et al. performed a multi-centre randomised study on extended oral anticoagulant therapy after a first episode of PE [17] to assess the long-term clinical benefit and the incidence of recurrence in this patient group. In 326 patients who had 3 months of anticoagulant therapy without recurrence or bleeding, they evaluated the clinical benefit of extending the course of therapy in patients with a temporary risk factor to 6 months and in patients with idiopathic pulmonary embolism to 12 months. Overall, 165 patients continued therapy of whom 15 had a recurrent venous thromboembolism (9.1% in 34.9 months) during two years of follow up and of 161 patients who stopped therapy, 18 had recurrent thrombosis (11.2% in 32.7 months). Interestingly,

efficacy was high during anticoagulant treatment since only one of the recurrences occurred during this period. However, a “catch-up phenomenon” occurred after discontinuation of therapy. Among patients with idiopathic venous thromboembolism 11 of 90 in the extended therapy group and 11 of 91 of discontinued therapy group suffered a recurrence (RR 0.99) The main conclusion was that patients with pulmonary embolism have a substantial risk of recurrence after discontinuation of treatment regardless of treatment duration of 3 or 12 months. This “catch-up phenomenon “could probably be avoided if anticoagulant therapy was to be continued indefinitely. Thus, the weighing of major bleeds induced against recurrences prevented becomes of paramount importance. This is even more important since the risk of recurrence apparently diminishes over time, stabilizing after 9 months independent of initial treatment duration. [18] whereas the risk of bleeding does increase with age and is not decreasing with prolonged anticoagulation, other than after the first few weeks on initiation of this treatment.

RECENT STUDIES ON INTENSITY

In order to investigate the safety in relation to efficacy of varying intensities of long-term secondary prophylaxis of thrombosis, two studies have recently been conducted. In the PREVENT study by Ridker et al [19] , 508 patients with idiopathic venous thromboembolism who had completed a full-dose anticoagulation therapy for a median duration of 6.5 months were randomly assigned to either placebo or low-intensity warfarin and subsequently followed for a period of 4.3 years (mean 2.1) .

Of 253 patients assigned to placebo, 37 had recurrent VTE (7.2 per 100 person years) and in the 255 patients in the low-intensity warfarin group 14 recurrences were found (2.6 per 100 person years), a risk reduction of 64% HR 0.36, CI 95% 0.19 to 0.67. Major bleeding occurred in two patients from the placebo group , 0.4% per 100 person year, and in eight patients in the warfarin group , 0.9% per 100 patient years; HR 2.53, CI 95% 0.49 to 13.03. Eight persons in the placebo group died as opposed to four in the warfarin group. Risk reductions were similar in all subgroups including those with inherited thrombophilia. The

overall conclusion was that low-intensity warfarin regimen is both efficacious and safe in comparison to placebo.

Kearon et al [20] compared low intensity warfarin therapy with conventional intensity warfarin in the prevention of recurrent venous thrombosis in the ELATE study. Out of 738 patients with idiopathic thrombosis who had completed three or more months of warfarin therapy, 369 patients were assigned to low intensity therapy (INR 1.5-1.9) and had 16 recurrences. (1.9 per 100 person years) Of the 369 patients assigned to conventional intensity therapy, 6 experienced a recurrence (0.7 per 100 person years), for a HR of 2.8, CI 95% 1.1 to 7.0. Major bleeding episodes occurred in 9 of the patients in the low intensity group (1.1 per 100 patient years) and in 8 of the patients in the conventional therapy group (0,9 per 100 patient years) , for a HR of 1,2, CI 95% 0,8 to 2,1. The mean duration of follow up was 2.4 years in both groups. The conclusion of this study was that conventional intensity warfarin therapy is more effective than low intensity warfarin and that low intensity warfarin does not reduce the risk of bleeding.

Many patients with APA and recurrent thrombosis receive warfarin aimed at an INR>3, based on results of a retrospective study [21-23]. Because an increase in the target INR is more likely to be associated with a higher risk of bleeding, Crowther et al [24] conducted a blinded randomized trial on the efficacy and safety of high-intensity warfarin (INR 3.1 to 4.0) versus moderate-intensity (INR 2.0 to 3.0) warfarin in patients with APA after a first episode of thrombosis. They followed a group of 114 patients over a period of 2.7 years. In the group of 56 patients receiving high intensity therapy 10.7% had recurrent thrombosis and in the group of 58 patients receiving moderate intensity therapy 3.4% suffered recurrence. The risk of major bleeding was slightly higher in the high intensity group: 3.6% per year versus 2.2% in the moderate intensity cohort. In conclusion, anticoagulant therapy targeted at the usual INR of 2.0 to 3.0 is appropriate for the prevention of recurrent thrombosis in patients with APA.

WARFARIN VERSUS LOW MOLECULAR WEIGHT HEPARIN

In patients with cancer the rate of recurrence after a first thromboembolic event is 3 times higher and the risk of bleeding complications is 6.2 times higher than in those without cancer. [25]. In order to improve treatment of thrombosis in patients with cancer, studies were conducted by Meyer et al. and Lee et al. [26,27] in which low molecular weight heparin (LMWH) was compared to vitamin K antagonists for the prevention of recurrent venous thromboembolism. In the larger of these two studies, 676 patients with acute thromboembolism were randomly assigned to two groups, one group of 338 patients received LMWH (dalteparin) at a dose of 200 IU per kg bodyweight and the other group of 338 patients was allocated to oral anticoagulant therapy (coumarin) with a target INR of 2.5. The two groups were similar in composition. Patients had solid tumours in 90% of the cases and 67% had metastatic disease. The probability of recurrence of VTE was 9% in the dalteparin group and 17% in the group assigned to oral anticoagulant therapy.

The risk of bleeding was 6% in the dalteparin group and 4% in the oral anticoagulation group (associated with INR above 3 in 50%). The mortality over the 6 month study period was approximately the same in both groups (39% LMWH, 41% coumarin) , the majority of which was due to progressive cancer (90%) . Meyer et al obtained similar results in a small group of patients with cancer (n=138). In the group of 71 patients who received warfarin, 15 (21.1%; 95% CI ,12.3-32.4%) experienced a major outcome event [major bleeding or recurrence] compared with 7 (10.5%) of the 67 patients in the group that received enoxaparin (95% CI, 4.3%-20.3%) ; p=0.09. There were 6 deaths due to bleeding in the warfarin group compared with none in the enoxaparin group. In the warfarin group, 17 (22.7%) patients died (95% CI, 13.8%-33.8%) compared with 8 (11.3%) in the enoxaparin group (95% CI, 5.0%-21.0%) ; p=0.07.

These data show that LMWH (i.e. dalteparin and enoxaparin) reduce the risk of recurrent VTE without an important increase in major bleeding as compared to vitamin K antagonists. In addition the use of LMWH might improve the quality of life in patients with cancer. The downside of LMWH-therapy is that it is costly and requires the ability of self-injection.

INDIVIDUALIZATION

Currently, the ACCP consensus is based on the mean optimal duration of therapy in large cohorts of patients and is mainly guided by the risk for recurrent venous thrombosis based on clinical characteristics. The patients' individual bleeding risk is not specifically taken into account. However, the individual risk of bleeding may differ based on age, sex, and comorbid conditions [28-30]. In addition, recent studies indicate that the presence of residual thrombosis assessed by ultrasonography and concentrations of D-dimer are predictive of the risk recurrence [10, 31, 32, and 33]

Vink et al [34] constructed a mathematical model, based on recent literature, in order to optimize the anticoagulant treatment strategy for individual patients in balancing the risk of recurrence against the risk of major bleeding complications. With the use of a formula the optimal duration of therapy can be estimated for each individual patient. Major drawbacks are that bleeding estimates are derived from one single study while the incidence of recurrence is also derived from a small number of studies. In addition, the influence on quality of life of recurrences, bleeding episodes and the treatment itself is not accounted for.

NEW DRUGS

The desire for a safe and easy manageable therapy as an alternative to warfarin for the long-term anticoagulant treatment has led to the development of new drugs. There are two promising new drugs that may prove to be more suiTable for extended prophylaxis than warfarin. Idraparinux is a long-acting pentasaccharide, inhibiting factor Xa. This drug needs only to be injected once a week. At a dose of 2.5 mg it has the potential to be as effective as warfarin and gave significantly less bleeding in a phase II trial [35].

Another newly developed drug, Ximelagatran, is an orally available pro-drug of the direct and reversible thrombin inhibitor Melagatran. This drug has been investigated for treatment of thrombosis in a placebo-controlled phase III trial. In this study [36] 1223 patients participated. After 6 months of initial conventional anticoagulant therapy, treatment was extended with either 18

months of placebo or 18 months of Ximelagatran. Ximelagatran proved to be far more effective than placebo and the incidence of recurrent events was reduced from 12% to 2%, for a HR of 0.16, 95% CI 0.09 to 0.30 without an increased risk of major bleeding. In patients receiving Ximelagatran a (transiently) elevated alanine amino transferase level in the early phase of Ximelagatran administration has been observed. The clinical relevance of this liver function disturbance is yet unknown.

CONCLUSION

Current recommendations for the duration of treatment of venous thromboembolism consider the presence of a (transient) risk factor, the extension of the thromboembolic event, concomitant cancer, presence of prothrombotic disorders and the number of previous events. Ideally, future therapy recommendations should also take into account the individual risk profile, including the bleeding risk, as well as intuitively attractive characteristics of the thrombotic / fibrinolytic balance in individual patients. These characteristics include residual thrombosis diagnosed by ultrasonography and the results of D-dimer laboratory tests. Recommendations on long-term duration of therapy are mainly based on studies on patients with deep venous thrombosis. Recent studies show that these recommendations can be safely extrapolated to patients that present with pulmonary embolism.

When vitamin K antagonists are used for the treatment of thromboembolism the dose should be adjusted to maintain an INR between 2.0 and 3.0. Lower intensities are less effective and not proven to be safer, while higher intensities are equally effective but cause more bleeding.

For cancer patients, low molecular weight heparin proves to be a better option than warfarin for the first 3 to 6 months of long-term treatment of deep venous thrombosis. Based on the results of recent studies patients with a first episode of idiopathic VTE should receive anticoagulant therapy for at least 12 months and indefinite anticoagulant therapy should be considered on an individual basis, taking into consideration the estimated risk of recurrent VTE, the risk of bleeding, the patient-compliance and patient-preference. When potentially

indefinite duration treatment is started a risk-benefit assessment for continuation should be performed regularly, e.g. at least once a year.

The future position of vitamin K antagonists will be challenged and therapy recommendations will change due to the development of new agents, which are as effective as the current anticoagulants but have a more sTable pharmacological profile and are potentially safer.

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Chapter 9

LOW MOLECULAR WEIGHT HEPARINS IN CANCER; REVIEW

MANAGEMENT AND PREVENTION OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH MALIGNANCIES

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ABSTRACT

Management and prevention of venous thromboembolism (VTE) in cancer patients is challenging. Not only is the risk of VTE in cancer patients elevated compared to patients without malignancies but standard treatment based on Vitamin K antagonists (VKAs) is less effective and is associated with an increased frequency of major bleeding.

Therapy with Low Molecular Weight Heparin (LMWH) is less sensitive to drug interactions, not hindered by a narrow therapeutic window and no monitoring is needed. LMWH therapy is therefore certainly more practical but may also prove to be more effective in these patients. Moreover a possible survival benefit has been claimed to exist by a number of investigators.

The underlying mechanism of which is not yet unravelled. A combination of cancer and thrombosis is a predictor of poor long-term survival. Hypercoagulability in cancer patients may indicate an aggressive change in the tumor and is associated with tumor progression. Hypercoagulability could also be a risk factor for developing cancer. Anticoagulant drugs, especially LMWH, may be of influence on tumor progression.

To assist clinicians in defining the role of LMWH in cancer patients, we categorized, summarized and critically weighed all available evidence on the subject. Based on available data derived from clinical trials certain recommendations on the application of heparins in oncological patients are made. Many uncertainties however remain regarding the subject of cancer related thrombosis in view of treatment and possible effects on tumor biology by heparins.

INTRODUCTON

Various population studies have shown an elevated risk for venous thromboembolism (VTE) in cancer patients. [1, 2, 3] Up to 7-fold increased risks as compared to patients without cancer have been found. [4] At the same time cancer patients are at much greater risk of complications when VTE occurs. Despite adequate treatment, recurrent events, bleeding and death are more common in this population. [2, 3, 5]

Over the last five years many reviews have been written on the subject of venous thromboembolism and cancer. They outline the use of primary and secondary thromboprophylaxis in distinct situations for variable periods of time. [6, 7, 8] Broad patient groups, medical as well as surgical, are evaluated [9, 10, 11] Effectivity and effect on survival caused by different therapeutic regimens have been assessed. [12, 13, 14] and insights are provided in pathogenetic mechanisms, such as tumor-specific clot-promoting mechanisms and hypercoagulability in cancer patients. [15, 16, 17]

We should realize however that regarding the therapeutic implications of LMWH in cancer patients, evidence underlying these reviews is derived from a limited number of relatively small original clinical studies in this specific group of patients. Indeed, most data presented is not derived from studies specifically designed to address oncological patients but is based on data from general patient populations leading to an unclear definition of the subgroup of cancer patients.

Considering the scarceness of original studies performed amongst cancer patients it is not surprising that conflicting opinions, especially in relation to survival benefits, are sometimes presented. [18, 19] This makes it often difficult for clinicians to base decisions concerning patient management on the literature at hand.

To assist clinicians in defining the role of LMWH in cancer patients, we categorized, summarized and critically weighed all available evidence on the subject. Finally, the remaining insecurities are listed and recommendations for future investigation are provided.

TREATMENT CHALLENGES

Patients with cancer are at increased risk of Venous Thromboembolic Events (VTE) compared to those without malignancy. [2] Blood is found to be hypercoaguable in the larger part of cancer patients. [20, 21] This hypercoagulability, however, does not predict subsequent development of thrombosis. Only a small portion of patients with signs of activated coagulation acquire a thrombotic event. [22]

Nevertheless, VTE is the second direct cause of death in cancer patients and is found in at least 50% of these patients at autopsy. [23, 24] Moreover, the combination of cancer and thrombosis in a patient is a predictor of poor long term survival. [3, 5] Activation of blood coagulation may be an indication of an aggressive change in the tumor itself. Direct or indirect activation of the coagulation cascade favors neoplastic dissemination and metastasis. A hypercoaguable state, on the other hand may very well be a risk factor for the development of cancer. [20, 25, 26] VTE sometimes is the first manifestation of malignant disease [27] an increased risk can be found for up to 10 years or more after the thromboembolic event. In addition to innate hypercoagulability associated with the harboring of cancer and added risk factors such as anti cancer treatment and immobilization, cancer patients have, assessed by routine venography, a doubled risk of developing a post operative thromboembolic complication following surgical procedures and a tripled increase in risk for fatal pulmonary embolism compared to patients without cancer. [28] Essentially all patients with cancer are candidates for prophylaxis when surgery is performed. Heparin prophylaxis lowers the incidence of VTE when assessed with venography from 30.6% to 13.6%. [29] Installation of prophylaxis in many cases however proves to be inadequate, in a historical cohort study the proportion of VTE that was potentially prevenTable was found to be two third of the patient population at risk. [30] The management of VTE is thus still far from optimal for oncological patients. [31] Retrospective studies [32, 33] revealed that high risks for VTE are found in patients with extended disease combined with anti tumor treatment, high age and hospitalization. All of those risk factors are cumulative. There is a higher risk in patients with brain, ovarian, pancreatic and gastric cancer. [4] Horton [34] made an effort for risk

stratification in patients with active cancer based on ACCP guidelines. [35] Currently however it is still not possible to define the exact risk for VTE in an individual cancer patient at any point in time. In case thrombosis does develop, both the risks for recurrence as well as major bleeding are increased. The main problem is the bleeding risk, correlating with extent of the disease varying from 2-3 times to a 5 times higher risk in moderate to extensive cancer. The risk of death following VTE is between two to eight times higher depending on gender and presence of chemotherapy. [36, 37]

Although the use of vitamin K antagonists (VKAs) is commonly associated with practical difficulties due to a narrow therapeutic window requiring regular laboratory monitoring, added management problems occur in cancer patients due to the disease itself and installed anti malignant treatment. [38]

Besides the fact that the recurrence rate is 2-3 fold increased [39, 40], a special therapeutic problem is posed by patients with recurrent episodes of venous thromboembolism during, well-regulated, warfarin therapy. [41]. Hence patients with cancer present a number of unique challenges in the treatment of thrombotic events and thromboprophylaxis.

PRIMARY PROPHYLAXIS

Generally, prophylaxis is installed to prevent VTE and its associated morbidity and mortality. While the incidence of thrombotic events and their impact is higher in cancer patients, there is at the same time an increased bleeding risk connected with installed anticoagulant therapy in oncological patients. Hence, the risks and benefits of treatment should be carefully taken into account when primary prophylaxis is considered.

A very important consideration is that the absolute reduction in symptomatic clinical events is much smaller than is suggested by venographical or otherwise objective tests. [42].

Hospitalized medical oncological patients

Hospitalized and debilitated cancer patients are at a much greater risk of developing VTE than cancer patients that are ambulant. The absolute risk depends on factors such as tumor type, stage or extent of cancer and whether or not anti tumor treatment is installed.

Prophylaxis with LMWH including fondaparinux can both safely and effectively lower the rate of VTE among acute general medical patients as shown in three large randomized controlled studies in which a reduction of VTE in the range of 50% was accomplished (overall 0.50 (95%CI 0.38-0.66)). However, of all patients included only between 5-14% were cancer patients. [43, 44, 45] (Table 1) Moreover, cancer specific risk factors are not reported. Based on the outcomes of these studies it is therefore not yet completely clear what the impact of prophylaxis on medical cancer patients is. Post hoc analysis for a group of 72 cancer patients from the Medenox study [46] showed that 40 mg enoxaparin daily reduced the VTE rate from 20% to 10% (NS) suggesting that on LMWH prophylaxis the incidence of VTE can be lowered equally effective in this specific group of medical cancer patients. However, there are no data for bleeding complications in this subgroup. Also, it is still unclear if the conclusions drawn from the studies that are performed hold true for all types of malignancy and if they are independent of presence or absence of chemotherapeutic regimens.

In general, cancer patients that are hospitalized or bedridden are more likely to benefit from prophylaxis than ambulatory patients. Of all cases of in-hospital VTE, 54% is found in general medical or non-surgical oncological patients [47]

The ACCP recognizes that hospitalized cancer patients are at a high risk of developing VTE and advices for these patients prophylaxis appropriate for their current risk state (Grade 1A) , reference is made to the surgical subsections in which treatment with LMWH once daily or UFH 3 times a day is recommended for two weeks. There is however a gross underutilization of thromboprophylaxis in hospitalized medical patients in spite of recommendations according to consensus [48]. Prophylactic treatment is used routinely by only 50% of medical oncologists [31]; whenever prophylaxis is used in cancer patients, this will most frequently consist of LMWH therapy.

Table 1. *Randomized, LMWH versus placebo controlled, double blind trials in medical patients*

Hospitalized oncological medical patients						
	Total no patients	Cancer patients	**LMWH**/ placebo	Dose/type/duration	Safety (major bleed)	Efficacy (incidence VTE)
					For all medical patients	
			56	20 mg enoxaparin	**0.3%**	**15.0%**
Medenox [45]	1102	157(14.3%)	**45**	40 mg enoxaparin 14 days	**1.7%**	**5.5%**
				placebo	1.1%	14.9%
			56			
Prevent [43]	3706	190(5.2%)	**85**	500IU dalteparin, 14 days	**0.16%**	**2.77%**
			105	placebo	0.49%	4.96%
Artemis [44]	849	131(15.4%)	**62**	2.5mg fondaparinux, 6-14 days	**0.2%**	**5.6%**
			69	placebo	0.2%	10.5%

Bold is either LMWH therapy arm of trial or treatment under investigation. Non-bold is comparator (either placebo or control drug).

Ambulant medical oncological patients

Not only hospitalized cancer patients can benefit from prophylactic anticoagulant treatment. There is also an increased risk for developing thromboembolic processes in ambulatory medical oncological patients undergoing combination therapy with chemotherapeutic agents and for instance Thalidomide. For this specific group of cancer patients it has been shown in an open label, non-randomized study, that the incidence of VTE can be effectively lowered on prophylactic LMWH treatment. [49] (Table 2) This is the only study on LMWH as a prophylactic drug in ambulant medical patients.

In stage IV breast cancer patients receiving chemotherapy long term prophylaxis with low dose warfarin had previously shown to be safe and effective for the prevention of thromboembolic complications. Low dose warfarin until 1 week after the end of chemotherapy, gave a relative risk reduction for objectively confirmed VTE of 85% (p=0.03). [50] Despite the outcome of this study low dose warfarin is neither recommended nor routinely used in outpatients receiving chemotherapy, essentially because the risk of bleeding on warfarin equals the risk of acquiring VTE without treatment. [51]

Table 2. *Non-randomized, LMWH versus placebo, in two consecutive study arms.*

Ambulant oncological medical patients on chemotherapy(CT) with added Thalidomide(Th)						
	Total no cancer patients	Concomitant therapy	**LMWH**/ placebo	Dose/type/duration	Safety (major bleed)	Efficacy (incidence VTE)
Zangari[49]	Arm1 256 (34%)	Placebo Th +C	87	placebo	No report on bleeding	34.5%
	Arm2 130(52.3 %)	**LMWH Th +C**	**68**	Enoxaparin 40 mg During chemotherapy		**14.7**%

Bold is either LMWH therapy arm of trial or the treatment under investigation. Non-bold is comparator(either placebo or control drug)

Surgical oncological patients

Among patients undergoing surgery those with active malignancy are at the highest risk for thromboembolic events, varying between 20-40%, as assessed by venography. The risk of pulmonary embolism is estimated at 1 %. [52]. This high risk can be attributed to a number of factors such as a preexistent hypercoaguable state and concomitant anti tumor therapy. In addition, surgery performed in oncological patients often more extensive and associated with prolonged immobility. [11]

Initial prophylaxis in surgical oncological patients

The first trial that specifically focused on thromboprophylaxis in cancer patients was conducted in patients undergoing colorectal surgery [53]. The LMWH enoxaparin (40 mg once daily) was compared with UFH (5000 IU 3 times a day) in 631 cancer patients undergoing elective abdominal surgery. LMWH was continued for 7 to 10 days postoperatively. The control group received UFH for the same period of time. VTE was documented by bilateral venography or pulmonary scintigraphy on day 7-10.

No difference in efficacy was detected between the two groups. (14.7% versus 18.2%). The Canadian colorectal DVT prophylaxis trial also failed to find a statistically significant difference between UFH and LMWH in efficacy and

bleeding. In a subgroup of cancer patients there was a trend favoring LMWH. [54]

In 2048 patients undergoing high risk abdominal surgery fondaparinux 2.5 mg was compared to dalteparin 2500 IU for initial prophylaxis. Both for major bleeding as well as incidence of VTE no significant difference could be found between the two therapeutic regimens. [55] In a subgroup analysis of 1408 cancer patients however fondaparinux compared favorably to dalteparin. VTE was reduced from 7.7% (55/712) in the dalteparin group to 4.7% (33/696) in the fondaparinux group. (OR 40.5% 95%CI -61.9-7.2 p= 0.02) while non cancer patients favored dalteparin. The overall risk for major bleeding was 3.4% on fondaparinux versus 2.4% on dalteparin. (p=0.122) Bleeding rates were almost identical in the subgroup of cancer patients. (Table 3)

Table 3. *Primary prophylaxis with LMWH in surgical oncological patients*

Initial prophylaxis with LMWH in abdominal surgery, randomized ,controlled clinical trials						
Study/author, Year,[ref]	Total no patients	Cancer patients	Therapy	Comparator	Safety (major bleed)	Efficacy (incidence VTE)
Enoxacan RCT, 1997[53]	631	631(100%)	40 mg enoxaparin once daily. Start 2h before surgery	UFH 5000 IU 3 dd	For all patients undergoing abdominal surgery No difference In bleeding complications	**14.7%** 18.2%
Mc Leod RCT, 2000[54]	936	475(50.7%) (**234**/241)	40 mg enoxaparin once daily. Start 2h before surgery till 10 days after	UFH 5000 IU 3dd	**2.7%** 1.5%	**9.4%** 9.4%
Pegasus RCT, 2005[55]	2048	1941(94.7%) (**954**/987)	2.5 mg fondaparinux once daily. Start 6h after surgery till 5-9 days	Dalteparin 2500 IU once daily 2h before surgery till 5-9 days	**3.4%** 2.4%	**4.6%** 6.1%

Bold is either LMWH therapy arm of trial or treatment under investigation. Non-bold is comparator.

More recently the efficacy and safety of nadroparin 2850 IU versus enoxaparin 40 mg were compared in a randomized study in patients undergoing colorectal surgery for cancer. In 950 evaluable patients the VTE rate detected by bilateral venography was 15.9% (74/464) on nadroparin and 12.6% (61/486) on enoxaparin, the rate of symptomatic VTE however was lower in the nadroparin treated group. (0.2% versus 1.4%). There was significantly less major bleeding in nadroparin treated patients. (7.5% versus 11.5%). [56] Installation of prophylaxis in high risk abdominal surgery is no longer subject to debate. The clinical trials conducted in this specific group of oncological surgical patients are therefore focused mainly on improving therapeutic regimens. For gynecological malignancies a number of small studies have been performed concluding that both UFH as well as LMWH are effective in preventing DVT when compared to placebo. [57] Both agents seem equally effective.

Craniotomy for central nervous system malignancies has an extremely high risk for thrombosis and is associated with VTE risks as high as 60% immediately postoperative and risks of 23% after one year. [58] A small number of randomized clinical trials have been performed looking at risk reduction on LMWH.

One study randomized 485 patients to either nandroparin or placebo starting between 18 and 24 hours after surgery. DVT was detected by bilateral venography in 26.3% of patients assigned to placebo and in 18.7% of the patients on LMWH. (OR 0.65 95% CI 0.39-1.07) There was no significant difference in major bleeding events. [59] Another study found a significant decrease in VTE in patients undergoing elective neurosurgery receiving enoxaparin 40 mg once daily in conjunction with the use of compression stockings for at least seven days beginning 24 hours after surgery. Twenty two out of 130 patients receiving enoxaparin, and who had venographic studies adequate for analysis, developed signs of VTE (17%) versus 42 out of 129 patients on placebo (33%). No differences in bleeding or overall mortality were found. Primary endpoint was symptomatic, objectively confirmed venous thromboembolism or deep vein thrombosis assessed by bilateral venography which was performed in all patients on day 8 ± 1. [60] A similar study**,** in 100 patients undergoing craniotomy, of which approximately 60% for brain tumors,

compared 5000 IU UFH every 12 hours to dalteparin 2500 IU once daily, beginning during operation and continued for 7 days or until patients were ambulant. Patients underwent duplex ultrasonography 1 week after surgery and 1 month of clinical follow-up. All patients were treated with intermittent pneumatic compression devices. There was no significant difference in postoperative hemorrhage or venous thromboembolism between heparin and dalteparin. [61] (Table 4)

Table 4. *Initial prophylaxis with LMWH in surgical oncological patients*

Initial prophylaxis in brain surgery, randomized, controlled clinical trials						
	Total no patients	Cancer patients	Therapy	comparator	Safety (major bleed)	Efficacy (incidence VTE)
Nurmohamed RCT, 1996 [59]	485	484(100%) (**241**/244)	nandroparin 7500 IU once daily 18-24h after surgery till 10 days	placebo	For all patients undergoing brain surgery **2.5%** 0.8%	**18.7%** 26.3%
Agnelli RCT, 1998 [60]	307	299(97%) (**150/**149)	Enoxaparin 40 mg once daily 24h after surgery till 7-10 days	placebo	**3%** 3%	**17%** 33%
Mc Donald RCT, 2003 [61]	100	63(63%) (**35**/28)	Dalteparin 2500 IU once daily at surgery till 7 days	UFH 5000 IU 2 dd	**0%,** 2%	**4%,** 0%

Bold is either LMWH therapy arm of trial or the treatment under investigation. Non-bold comparator (either placebo or control drug)

A study comparing two different prophylactic regimens, enoxaparin 40 mg once daily versus heparin 5000IU bid, in 150 patients undergoing craniotomy for brain tumor did not show any significant difference between the two treatment groups, probably because the study was underpowered. [62]

A meta-analysis on LMWH for the prevention of VTE in neurosurgery demonstrated that the relative risk of developing a thrombotic event can be

reduced by almost 40% on prophylaxis with LMWH ($p<0.001$), without an excessive increase in bleeding. [63] Despite the fact that well conducted randomized controlled studies have shown that LMWH is effective and safe in the neurosurgical setting, prophylaxis still is not widely used by neurosurgeons because of fear of intra cerebral hemorrhage. [64]

Apart from abdominal, gynecological and neurological oncological surgery other oncological settings are sparsely studied.

The ACCP recommends based on sound evidence that cancer patients undergoing surgical procedures receive prophylaxis that is appropriate for their current risk state. (Grade 1A) Both LMWH once daily and UFH three times a day are equally effective and safe for the prevention of DVT in surgical patients [65].

Prolonged prophylaxis in surgical oncological patients

The ENOXACAN II study was designed to determine the safety and efficacy of extended prophylaxis with enoxaparin 40 mg once a day given for 21 days versus enoxaparin for 6-10 days in cancer patients. Patients receiving prophylaxis beyond hospitalization had a reduced rate of VTE by 60%. (95 CI 10-82%) on bilateral venogram 25-31 days post operatively. There was no difference in bleeding. [66]

In a very recent study outcomes were also improved by prolonging prophylaxis with LMWH in 590 patients undergoing major abdominal surgery.[67] Overall, patients receiving 1 week of dalteparin 5000 IU a day had 16.3% VTE versus 7.3% in the group treated for 4 weeks. (RR 0.45 95%CI 0.24-0.83 p= 0.01) The subgroup of 198 cancer patients showed the same effect, (19.6% versus 8.8%, RR 0.45 95% CI 0.21-0.96 p= 0.03) suggesting that prolonged therapy with LMWH after surgery for malignancy reduces the incidence of VTE without increasing the risk of major bleeding. (Table 5).

A common weakness of studies thus far is that assessment of efficacy of prophylaxis is based on reduction of asymptomatic, venographically confirmed DVT and not on clinically significant VTE following cancer surgery.

In selected high-risk general surgery patients including those who have undergone major cancer surgery, the ACCP suggests post-hospital discharge prophylaxis with LMWH. (Grade 2A).

Table 5. *Prolonged prophylaxis with LMWH in oncological surgical patients*

Prolonged treatment with LMWH in abdominal surgery						
	Total no patients	Cancer patients	Therapy	comparator	Safety (major bleed)	Efficacy (incidence VTE)
					All patients undergoing surgery	
Enoxacan II RCT, 2002 [66]	332	332 (100%)	40 mg enoxaparin once daily for 19-21 dys	40 mg enoxaparin once daily for 6-10 dys	**0.4%,** 0%	**4.8%,** 12%
FAME RCT, 2006 [67]	343	198 (58%)	Dalteparin 5000 IU once daily for 4 weeks	Dalteparin 5000 IU for one week	Bleeding not increased	**8.8%** 19.6%

Bold is either LMWH therapy arm of trial or treatment arm under investigation. Non-bold is comparator (either placebo or control drug).

SECONDARY PROPHYLAXIS

The recommended treatment for acute venous thromboembolism consists of initial therapy with oral anticoagulation together with LMWH or UFH for at least 5 days followed by long term therapy with an oral anticoagulant continued for at least 3 months. In patients with cancer however on one the hand oral anticoagulant treatment is associated with a higher rate of recurrence and increased frequency of major bleeding. [36] On the other hand recent meta-analysis comparing UFH with LMWH showed a 40% reduction in mortality rate among cancer patients receiving LMWH. [68] LMWH may therefore be an attractive alternative for secondary prophylaxis in cancer patients

The relentless nature of VTE in oncological patients and the high risk of bleeding are the two most important factors to be considered when anticoagulant treatment is initiated. There is a higher complication rate due to an altered response to anticoagulant medication resulting from co-morbidity and

cancer associated hypercoagulability. Despite treatment patients with cancer and VTE have a higher mortality rate than patients with cancer alone. [1] This may be attributed to an association of VTE with more aggressive malignancies resulting in increased mortality due to thrombotic complications and advanced disease. For prolonged therapy the higher failure rate of therapy based on vitamin K antagonists in patients with cancer may be mainly due to difficulties in maintaining a therapeutic medication level. The highest incidence of major bleeding in cancer patients however is found with sub-therapeutic medication levels [37] On the other hand VTE can occur while on adequate therapy. When VTE occurs during oral anticoagulant therapy it can be continued at a higher intensity, or a switch can be made to UFH, vena cava filter or LMWH. The majority of cancer patients that develop recurrent events while on warfarin therapy can be successfully managed on long term dalteparin therapy. [41] With LMWH therapy a constant therapeutic effect can be achieved without laboratory monitoring. Comparisons between LMWH and warfarin for long term therapy have only been made in small studies, primarily consisting of patients without cancer. Overall, a non significant reduction of the risk for recurrence of 30% and a reduction in bleeding risk of 62% were found. [69, 63] More recently, studies on optimalization of therapy have been conducted especially designed for cancer patients.

In the CLOT study 676 cancer patients of whom 67% with metastatic cancer were either treated with dalteparin or warfarin. One group of 336 patients was treated with 1 month of dalteparin 200 IU/kg once daily, followed by 4 weeks dalteparin at 75-80% of this dose; the other group of 336 patients received initial 5-7 days of dalteparin 200 IU/kg combined with vitamin K antagonists until therapeutic levels were reached, followed by vitamin K antagonist alone.

Dalteparin significantly reduced the risk of symptomatic recurrent thrombosis by 52%, from 17% (53/338) to 9% (27/338) HR 0.48 p=0.002. No difference was found neither in bleeding nor mortality rate. (6% bleeds on dalteparin, 4% warfarin and 39% died in each group) [70].

The CANTHANOX study compared in 147 cancer patients the therapeutic properties of enoxaparin and warfarin. One group of 71 patients received 3 months of therapy with enoxaparin 1, 5 mg/kg once a day the other 75 patients

were initially treated with enoxaparin followed by warfarin therapy. No significant differences in recurrent VTE or bleeding could be claimed, because the study was underpowered. There was however a trend towards a higher risk of recurrence, bleeding and mortality in the warfarin group.
(Recurrence (15/75) 21% and (7/71) 10.5%, p=0.09, bleeding (12/75) 22% and (5/72)11.3%, p=0.07, major bleed 16%, 7%, p=0.03, mortality 38.7% on warfarin, 31% on enoxaparin, respectively). Conclusion LMWH is as effective as and possibly safer than warfarin in cancer patients. [71] (Table 6)

Table 6. *Prolonged prophylaxis with LMWH in oncological surgical patients*

Randomized,controlled clinical trials comparing LMWH with coumarin						
Author, year, [ref]	Patient total	LMWH versus comparator	Criteria fulfilled (see legend)	Tumor type	Safety (major bleed)	Efficacy (incidence VTE)
LEE RCT, 2003 [70]	672 (336/336)	200 IU/kg dalteparin for 1 month followed by 150 IU/kg for 5 months	1,2,3,4,5,6,7	88% solid	6%	8%
		Coumarin(INR 2.5) for 6 months			4%	15.7%
Meyer RCT, 2002 [71]	138 (67/71)	1.5 mg/kg enoxaparin for 3 months	1,3,5,6,7	100% solid	7%	10.5%
		Coumarin (INR 2.5) for 3 months			16%	21.1%

Legend 1. Primary focus on cancer patients 2. Concomitant antineoplastic therapy started. 3.surgical procedures included. 4. Mobility scored. 5. Median patient survival measured. 6. Recurrent event objectivated according to standard. 7. Major bleeding recorded according to standard. Bold is either LMWH therapy arm of trial or the treatment under investigation. Non-bold is comparator (either placebo or control drug)

Based on these studies the use of LMWH for the secondary prevention of VTE should be preferred over vitamin K antagonists in cancer patients, because there is strong evidence that LMWH is effective and safe for preventing recurrent VTE in cancer patients. There are no reports of excess bleeding.

Relative efficacy and safety of LMWH and UFH have not been properly investigated in patients with cancer. However, looking at subgroups of cancer patients both appear to be similar in efficacy. [72, 73, 74, 75]
The duration of therapy has not yet been adequately addressed in cancer patients. It is acknowledged that the risk of thrombosis is increased in the presence of any ongoing risk factor. Patients without metastases are therefore treated for as long as the cancer is active or while receiving anti tumor therapy. Patients with metastases continue on indefinite therapy. The ACCP does not give specific recommendations for long-term anticoagulant therapy in cancer patients. Usual practice however is indefinite anticoagulation because most patients have advanced disease at the time of the thrombotic event.

SURVIVAL

In oncological patients activation of coagulation is frequently uncovered. This hypercoaguable state is associated with tumor progression. [76]
LMWH therapy may favorably affect the progression of malignancy. An important reduction in mortality was first observed in a subgroup analysis of cancer patients on nadroparin for the treatment of VTE. [77] The positive effect of LMWH on survival in cancer patients without VTE has also been evaluated. When installing prophylactic treatment for the mere cause of prolonged survival special attention should be awarded to the prevention of clinically relevant major and non-major bleeding.

Positive effects on survival in cancer patients due to anticoagulant treatment have been claimed to exist for different types of anticoagulants by a number of investigators. One of the earliest studies demonstrated that warfarin therapy was associated with a significant prolongation of progression free and overall survival in patients with small cell lung cancer. In other tumor types however no survival effect was found. [18] Prolonged warfarin therapy in patients with VTE and without apparent malignancy from 6 weeks to 6 months was associated with a reduced incidence of newly diagnosed cancer. After 6 years of follow up 50% more patients developed cancer in the 6 week treatment group. [78] Systemic reviews concluded that there is no convincing evidence of a

beneficial effect for warfarin or UFH on survival in cancer patients. [19, 79] Heparin however appears to impart prolonged survival in cancer patients with acute DVT. A prospective study evaluating the influence of heparin on long-term survival in patients with small cell lung cancer undergoing chemotherapy found an increase in response to chemotherapy (24%-37%) as well as an increase in survival (261-317 days) in the group of patients who received 5 weeks of UFH .[80]

Two observational studies have also suggested improvement of prognosis, when LMWH is used: one for patients with advanced hormone-refractory prostate cancer and another for malignant melanoma. [81, 82]

Several post hoc studies have found a beneficial effect of short course treatment with LMWH on survival of cancer patients with VTE. [68, 83]

In contrast, a meta-analysis by Feretti showed a statistically significant decrease of VTE and bleeding in favor of LMWH, but no difference in mortality. [84]

More recently four studies have been conducted, focused mainly on LMWH with respect to survival benefit. In the small cell lung cancer study, dalteparin was compared to UFH. The median progression free survival of patients improved significantly in patients receiving LMWH in addition to chemotherapy compared to patients receiving chemotherapy alone. This was the case for patients with extensive disease as well as limited disease**.** [85]

In the FAMOUS trial, patients with advanced stage malignant disease of breast, lung, genitourinary tract, gastrointestinal tract, pancreas or liver received either dalteparin 5000IU for 12 months or no therapy. The primary endpoint was survival at 1 year. The placebo group survival 1, 2 and 3 years were 42%, 19% and 13% respectively. For the dalteparin group this was 45%, 27% and 21%.

Dalteparin was not associated with improved survival after one year. There was however an improved survival beyond 17 months in the group receiving dalteparin. This suggests a long term biological effect of dalteparin**.** [86]

The malignancy and LMWH therapy trial (MALT) in patients with advanced cancer divided 249 patients into two groups. One group received nandroparin for 2 weeks followed by 4 weeks of half dose therapy. The other group received placebo treatment for 6 weeks. There was no significant difference found during the first six months of follow up. Extended follow up revealed a survival

benefit in the nadroparin group. (7.7 months versus 5.5 months, p=0.024) This beneficial effect was mainly attribuTable to a subgroup of patients who exhibited better prognosis at study entry (16.5 months versus 7.4 months p=0.019) [87] (Table 7).

Table 7. *LMWH therapy and survival in oncological patients without VTE*

Study [ref]	Patient number n/n (%)	Criteria fulfilled	Therapy	Period of Follow up	survival (%)	Median Survival (months)	Safety (major bleed)
MALT [87] RCT	148/302 (49 %)	All	Nadroparin 6 weeks	1 year	39%	8.0 #	3 %
	154/302 (51%)		placebo	idem	27%	6.6	1%
FAMOUS [86] RCT	190/374 (51%)	All	Dalteparin 1 year	until death, 1,2, 3 year estimates	1=46%, 2=27%, 3=21%	43.5 (ns)	0.5%
	184/374 (49%)		placebo	idem	1=41% 2=18% 3=12%	24.3	0%
SCLC [85] RCT	42/84 (50%)	All	CT(chemo) + Dalteparin 5000 IU 18wks	Until death Median of 10 months (2-33) estimates	1=51.3% 2=17.2%	13.0 *	0%
	42/84 (50%)		CT alone	idem	1=29.5%2 =0%	8.0	0%

*Legend: 1. primary survival study 2. cancer primary focus 3. tumor type defined 4. concomitant therapy defined 5. mobility scoring system 6. bleeding according to standard .# p=0.021, ns= not significant, * p=0.0*

Post hoc analysis of the CLOT study results showed no difference in survival for the overall study population. However in a subgroup of 150 patients with non metastatic solid tumors a survival benefit was found. The cumulative mortality was 20% for patients treated with nadroparin and 35% for those treated with warfarin. [88] A review of pooled data of studies treating a total

1726 patients for at least 3 months with LMWH reported no survival benefit of LMWH over warfarin (327 died, 160 patients (48.9%) in the LMWH group versus 167 patients (51%) in the warfarin treatment arm, OR 0.95 95%CI 0.73-1.23,p=0.67) [89].

The ACCP does not recommend LMWH for the sole purpose of prolonged survival. There is however a trend towards a beneficial effect of LMWH. The effect is most pronounced among patients with limited disease. There is a possibility that certain tumor types may be more responsive to LMWH therapy than others.

WHY COULD LMWH HAVE ADVANDTAGE OVER OTHER ANTICOAGULANT DRUGS?

Cancer and thrombosis are consistently linked. There is an increased risk of VTE in cancer patients, caused by activation of the coagulation system due to procoagulant properties of malignant cells. [20] Following an episode of VTE on the other hand an increased risk of cancer can persist for several years. [77,24] Positive effects on patient survival after treatment for VTE have been found in cancer patients for both warfarin as well as heparin. [18,70,71] Also in cancer patients without VTE a positive effect on survival due to treatment with anticoagulant drugs has been observed. [86,87]

Tumor cells have the ability to activate blood coagulation. Tissue Factor (TF), thrombin, fibrin, and proteins that regulate the fibrinolytic system such as urokinase and plasminogen are directly involved in tumor growth and dissemination. [90]

Anticoagulant drugs may therefore very well influence tumor progression. The anti tumor properties of heparin were first observed in an experimental animal study [91] and later confirmed by others. [80,92]

Biological mechanisms for the anti tumor effect of heparins are diverse and consist besides inhibition of coagulation activation and fibrin formation also of coagulation independent effects such as impairment of tumor cell adhesion, inhibition of angiogenesis, inhibition of tumor cell heparinase activity, induction of apoptosis and immune system modulation. [93]

The link between angiogenesis and the haemostatic system seems to be mediated by TF. Tumor cell derived cytokines can induce TF expression and reduce thrombomodulin inducing a pro-thrombotic state. Thrombin acts as a potent growth factor for malignant cells. On the whole there is an over expression of TF. [94] Heparins bind and potentiate anti thrombin III, inducing the release of tissue factor pathway inhibitor (TFPI) from endothelium. [95], thus inhibiting TF and thereby the adhesion of tumor cells to platelets by blocking p-selectin and inhibition of tumor cell heparinase. [96] Heparinase facilitates tissue invasion by inducing the release of angiogenic factors and causing capillary growth. The activity of heparinase correlates with the metastatic potential of the cancer cell. [97] The TF/f VIIa complex upregulates urokinase receptor and receptor insertion in cell surface enhancing tumor cell migration and invasion. The TF/f VIIa complex also induces VEGF expression enhancing angiogenesis. Tumors have different expression of the 3 major VEGF forms (VEGF 189, VEGF165 and VEGF121) VEGF 189 and VEGF 165 bind heparin with high affinity. The expression of a VEGF type that binds with less affinity to heparin in tumors such as breast cancer and melanoma makes it less likely that the tumor will respond to heparin, whereas in tumors with high affinity VEGF such as astrocytoma a better response can be expected. [98] The inhibition of angiogenesis is potentially anti oncogenic because it deprives the tumor cell of blood supply necessary for growth and metastasis.

LMWH can hinder growth factor binding sites to a greater degree than UFH. They furthermore have a prolonged half life and an increased bioavailability compared to UFH. [99] Heparins also play a role in the regulation of cytokines involved in immune destruction of cancers. There is a direct effect of heparins and LMWH on extravasation of leukocytes hereby enhancing the susceptibility of cancer cells to immunologic attacks.

Tumor cell degradation is mediated by natural killer cells and enhanced by tumor necrosis factor (TNF) and interferon (IFN); continued heparinization enhances the activity of TNF and IFN. [100]

Currently, inhibition of p-selectin mediated platelet coating of tumor cells during the initial phase of the metastatic process is seen by many as a major

mechanism of heparin in cancer. Platelet aggregation and fibrin coagulation are responsible for protection of tumor cells from destruction by natural killer cells. In summary while there are many potential mechanisms in which heparins may influence tumor biology, the exact mechanism directly responsible for the different clinical effects between LMWH and UFH that have been observed are not yet unraveled. For the time being our judgment is therefore essentially based on clinical evaluation.

CONCLUSIONS

Based on available data, derived from clinical trials performed throughout the years, certain recommendations on the application of heparins in oncological patients can be made.

Primary prophylaxis

- Hospitalized medical oncological patients are at high risk of developing VTE, prophylaxis with LMWH once daily or UFH 3 times a day is recommended during hospitalization.
- The incidence of VTE can be effectively lowered on prophylactic LMWH treatment in ambulant medical oncological patients undergoing combination therapy with chemotherapeutic agents and for instance thalidomide.
- Prophylactic low-dose warfarin is not recommended in ambulant medical oncological patients because the risk of bleeding on warfarin equals the risk of VTE without installed therapy.
- Initial prophylaxis in cancer patients undergoing surgical procedures is well established for abdominal, gynecological and colorectal surgery. There is no significant difference in efficacy and bleeding between UFH and LMWH.
- Initial prophylaxis with LMWH in cancer patients undergoing brain surgery is both safe and effective.
- prolonged post-hospital therapy with LMWH after major cancer surgery reduces the incidence of VTE without increasing the risk of major bleeding.

Secondary prophylaxis

- The use of LMWH or UFH in treatment of VTE in cancer patients with solid tumors is preferred over vitamin K antagonists and significantly reduces the risk of recurrent thrombosis, without implications for bleeding or mortality rate.

Survival

- There is no convincing evidence for a beneficial effect for warfarin or UFH on survival in cancer patients.
- The median survival improves significantly in patients in patients with small cell lung cancer receiving LMWH in addition to chemotherapy compared to chemotherapy alone.
- There is a beneficial effect of LMWH therapy in cancer patients with non metastatic solid tumors. Certain tumors may be more responsive to LMWH therapy than others.
- The ACCP does not recommend LMWH for the sole purpose of prolonged survival.

Uncertainties

Despite of the available data on the subject of cancer related thrombosis still many uncertainties in view of treatment and possible effects on tumor biology by heparins and LMWHs remain. Lingering insecurities enclose uncertainties considering the duration of anticoagulant therapy. The optimal duration of therapy is not yet adequately addressed in cancer patients. Long term therapy with LMWH may be in order as the risk of VTE is increased in the presence of any ongoing risk factor. Specific risk profiles for different types and stages of cancer towards bleeding risks and uncertainties about therapeutic side effects such as the increased incidence of osteoporosis are not yet sufficiently explored. Furthermore the interaction between a pro-thrombotic state and subsequent development of cancer and the exact mechanisms of action responsible for the observed effects on survival of LMWH in certain oncological patients is not unambiguously clear. For newly developed anticoagulant drugs such as direct anti-Xa inhibitors and Thrombin inhibitors no specific data on prophylaxis, treatment of VTE or survival benefit are available in oncological patients. Intuitively, anticoagulant drugs with a sTable and predicTable performance profile that can be administered orally are in a long- term therapy setting to be preferred over parenteral administered drugs.

Future research

Future research should consider large cohorts of cancer patients that are sufficiently characterized. New as well as current anticoagulant drugs need to be tested, for their antithrombotic properties, anti tumor properties and effects on survival, both in clinical trials as on a more fundamental biological level.

Individual risk assessment models ought to be developed taking into account tumor specific properties such as tumor type, stage or extent of cancer, concomitant anti cancer treatment as well as possible contra indications of anticoagulant therapy.

And last ,but not of the least importance, duration of anticoagulant therapy must be considered especially in relation to harmful side effects of therapy such as osteoporosis.

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Chapter 10

THROMBIN GENERATION IN PATIENTS AFTER ACUTE DEEP VEIN THROMBOSIS

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ABSTRACT

Thrombin generation measurement may be of value for assessing the risk of venous thromboembolism, but its long term profile has not been assessed in patients.

We evaluated thrombin generation by Calibrated Automated Thrombogram (CAT) in plasma during follow up of 104 consecutive patients after an acute episode of deep venous thrombosis. Blood was drawn 3 times over the course of 24 months. Thrombin generation was measured in absence and presence of thrombomodulin and compared to a reference range derived from thrombin generation curves in 137 healthy volunteers.

Thrombin generation of patients showed significantly higher endogenous thrombin potential (ETP) and peak height compared to the reference population. Differences were more pronounced in assays triggered with 1 pM TF. Inhibition by thrombomodulin was attenuated in patients off anticoagulants as compared to the reference population (21% versus 42.2%, $p<0.0001$); inhibition in patients on anticoagulant treatment was less pronounced (9.7%, $p<0.0001$).

Protein C activity, protein S antigen as well as free protein S showed highly negative correlation with ETP in all patients. A significant negative relation was found between FVIII levels and thrombomodulin induced reduction of ETP and peak height.

In conclusion, thrombin generation by CAT reflects changes in coagulation status in patients following a thromboembolic event and is most sensitive at CAT analysis triggered with 1 pM TF. A role for factor VIII as an important attribuTable cause of hypercoagulability is reflected by the reduced inhibitory effect of thrombomodulin at high factor VIII levels.

INTRODUCTION

Prevention of a recurrent event is the main objective of anticoagulant treatment for an acute thromboembolic process. The optimal duration of anticoagulant treatment remains a subject of debate [1] due to the inability to account for individual risk factors for recurrent thromboembolism. Several strategies can be employed to estimate risk of recurrence, including assessment of amount of residual thrombosis [2,3] , as well as coagulation activity after cessation of antithrombotic therapy by means of laboratory tests such as for D-dimer [4,5] or FVIII levels. [6,7,8] However, these laboratory assays reflect ongoing fibrinolysis rather than coagulation (D-dimer), while Factor (F) VIII levels only provide one element of the complex coagulation network. Similarly, determination of FXI, FIX and prothrombin could be utilized as risk indicators, since the levels of these proteins are also associated with risk of venous thrombosis. [9, 10]

Intuitively, a more global coagulation test that integrates the information retrieved from separate coagulation tests could potentially improve patient management. It has indeed been demonstrated that a global coagulation test such as the thrombin generation assay performed at one point in time can predict an increased risk of a first episode of deep venous thrombosis (DVT) in persons with an increased ETP, an increased risk of recurrence based on a high ETP however was not found. [11] On the other hand, a low chance of recurrence was found in patients after acute DVT with low ETP. [12] In addition, thrombin generation has been utilized to screen for thrombophilic defects. [13, 14, 15] Given these observations thrombin generation measurement may be a good candidate for the management of individual anticoagulant treatment in the secondary prevention of recurrent thrombosis in patients following an acute thrombotic event. Since the risk of recurrent thrombosis is not sTable in time, we were interested to study the variation in time of thrombin generation in patients after a DVT as compared to healthy individuals. In addition, we compared on and off anticoagulant treatment on thrombin generation with and without the addition of thrombomodulin (TM).

METHODS

Patients and reference population

Over the course of three years, 104 patients with acute DVT were identified and followed over time at the outpatient thrombosis clinic of the University Hospital Maastricht, Maastricht, the Netherlands. Patients were followed up for a period of 24 months following their diagnosis.

The inclusion of patients was consecutive and irrespective of the fact whether an event was a first event or a recurrent event and whether this event was idiopathic or provoked. In all patients DVT was confirmed by ultrasound at the first visit. The study was approved by the local ethics board and written informed consent was obtained for additional blood collection in order to test thrombin generation.

Anticoagulant treatment was installed according to ACCP guidelines [16]. For a number of patients treatment was tailored individually. Blood was drawn 1 month after cessation of treatment in 72 patients, for patients with provoked thrombosis this meant that blood was drawn at month 4 and for patients with idiopathic thrombosis blood was drawn at month 7 (B1: 4-7 months). The second round of laboratory tests was performed for the entire group off anticoagulant treatment (65 patients) at 12 months (B2) and the third at 24 months in 40 patients (B3). While the study was and is still ongoing at the moment of analysis not all of the patients had reached the end of the two year follow-up period. The Thrombin Generation assay was preformed in March 2007 on all available samples to the date of 12 December 2006 (only halfway during the third year of follow-up).

For patients on prolonged anticoagulant treatment the blood was also drawn at three points in time. The first blood draw took place at 6 months (32 patients) after the acute event, the second blood draw at 12 months (18 patients) and the final draw at 24 months (8 patients).

The reference laboratory values were derived from a group of 137 healthy individuals recruited from the community, frequency matched for sex and age and originating from the same region of the Netherlands. Healthy individuals on anticoagulant medication or on anti-platelet drugs were excluded as were pregnant women and women on oral contraceptives. Blood for the reference

laboratory values was drawn at two separate occasions that were 12 months apart.

Normal pooled plasma

Normal pooled plasma used for normalization of samples was prepared within the departments of Hematology and Clinical Chemistry of the University Hospital Maastricht, the Netherlands, by pooling plasma from 80-90 apparently healthy volunteers.

Blood collection and plasma preparation

Venous blood was collected in 3.2% citrate (w/v). Blood was drawn three times over the course of a two year follow-up period in all patients. Platelet poor plasma was prepared by two centrifugation steps: the first at 2000 g for 15 minutes and the second at 11000 g for 5 minutes. Plasma aliquots were snap-frozen in liquid nitrogen, stored at -80°C until use. All samples were thawed at 37°C for 15 minutes before analysis and analyzed batch wise.

Thrombin generation measurements

Thrombin generation in tissue factor (TF)-triggered platelet poor plasma was measured by means of the Calibrated Automated Thrombogram (CAT) method (Thrombinoscope BV, Maastricht, the Netherlands), which makes use of a low affinity fluorogenic substrate for thrombin (Z-Gly-Gly-Arg-AMC) to continuously monitor thrombin activity in clotting plasma. In order to correct for inner-filter effects and substrate consumption, each thrombin generation measurement was calibrated against the fluorescence curve obtained in the same plasma with a fixed amount of thrombin-α_2-macroglobulin complex (Thrombin Calibrator, Thrombinoscope BV), as recommended by the manufacturer. Fluorescence was read in an Ascent Reader (Thermolabsystems OY, Helsinki, Finland) equipped with a 390/460 filter set, and thrombin generation curves were calculated with the Thrombinoscope software (Thrombinoscope BV).

All samples were tested at the same occasion and thrombin generation was determined under three experimental conditions (final plasma concentrations): 1 pM TF and 4 μM phospholipids in the absence and presence of 2 nM soluble

thrombomodulin (TM), and 5 pM TF and 4 μM phospholipids. The TF triggers and phospholipids were obtained from Thrombinoscope BV; TM was kindly donated by Prof. Coen Hemker, Maastricht. No corn trypsin inhibitor (CTI) to inhibit contact activation was included in our samples, although several authors reported reduced variability by means of contact factor inhibition using CTI. [17, 18] Contact activation was extensively assessed at previous occasions in our laboratory by analyzing TG in the absence of TF and was never observed in plasma obtained and prepared according to the described protocol.
Three parameters were derived from the thrombin generation curves: lag time, peak height and endogenous thrombin potential (ETP, area under the curve). Data for these parameters were normalized towards and given as ratio to normal pool plasma, analyzed on each plate.
The intra-assay variation of the thrombin generation curve parameters was determined using platelet-poor plasma (PPP) from three different subjects assayed in 21 replicates per sample in one run. None of the concentration dependent parameters (ETP and peak) had a coefficient of variation (CV) > 5%. The lag time had a CV of 4-6%, for the other time dependent parameters CV was < 4%. The intra-assay with TM for all derived parameters was below 10%.

For determination of the inter-assay variation, two lots of normal pool plasma were analyzed in 21 independent runs over a period of one month using one lot of PPP-reagent, three different batches FluCa and substrate, and two lots of calibrator. For the concentration dependent parameters the CV was 7-8%, for the time dependent parameters 5-8 %. For the analysis with 1 pM TF and TM, the overall coefficients of variation are 5.93%, 14.68% and 15.44% for lag time, ETP, and peak height, respectively.
In order to test the inhibitory potential of the protein C pathway on thrombin generation TM was titrated to inhibit ETP by approximately 50% in normal pooled plasma triggered with 1pM TF.
Protein S (total) levels were measured with a homemade assay, containing Dako (ITK) antibodies, and validated in an external quality control program (ECAT, Leiden, the Netherlands). Free protein S levels were measured with the Asserachrom free protein S assay (Stago Diagnostics, Asnieres, France). The

FV Leiden mutation was determined with a commercial kit (Roche Diagnostics, Basel, Switzerland) on a Light Cycler instrument (Roche Diagnostics). FVIII activity, APC resistance and protein C activity assays were performed on a CA7000 Coagulation instrument (Dade-Behring, Eschborn, Germany) according to the manufacturer's instruction.
FVIII activity was measured with a one-stage clotting assay (Dade-Behring). APC resistance was measured with a ProC AC R kit (Dade-Behring) and protein C activity was measured with the Behrichrom protein C kit (Dade-Behring).

Statistical analysis

Data are expressed as mean [95% confidence interval; CI95%], unless otherwise specified. Differences between parameters of the different thrombin generation analyses (1 pM TF (with and without added TM) and 5 pM TF) were analyzed using paired Student's t test, whereas the differences between genders were analyzed using Student's t-test. Correlations were expressed as Pearson coefficients. A two-tailed probability value $P < 0.05$ was considered statistically significant. Statistics were computed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 104 consecutive patients were included in the study. They had a mean age of 55.8 years (range: 26- 83) and 53 (46.9%) were male. Of these patients 19% had a previous episode of DVT (and 24% a positive family history of venous thrombosis). Thrombin generation curves were measured for these patients and compared to a reference range derived from thrombin generation curves in 137 healthy volunteers. The mean age in the reference group was 53.7 years (22-90) and the number of males in this group was 67 (48.2%). During follow-up a number of patients remained on anticoagulant treatment for various reasons e.g. the presence of two or more previous thromboembolic events, substantial residual thrombosis on ultrasound, known combined or severe thrombophilic defects. (A total of 32 patients continued to be on anticoagulant therapy at 6 months, 18 at 12 months and 8 at 24 months.)

Table 1. Thrombin generation measurements at 1 pM TF, 5 pM TF and effect of TM at 1 pM TF in patients during follow-up compared to healthy individuals. Data are presented as normalized mean [95% confidence interval].

	Healthy individuals	Patients						
	HI	B1		B2			B3	
	(n=137)	(n=72)	*P*(B1-HI)	(n=65)	*P*(B2-1)		(n=40)	*P*(B3-1)
5 pM TF								
Lag time	2.6 [2.4-2.8]	2.4 [2.1-2.7]	NS	2.4	[2.1-2.5]	NS	2.1 [1.9-2.2]	NS
ETP	102.9 [96.6-109.2]	112.3 [103.1-121.6]	NS	121.2	[112.7-129.7]	<0.05	119.0 [109.8-128.2]	<0.0001
Peak height	93.6 [89.7-97.5]	121.2 [111.4-131.1]	<0.01	128.3	[119.5-137.1]	<0.05	130.5 [122.4-138.6]	<0.01
1 pM TF								
Lag time	4.0 [3.9-4.1]	5.6 [4.8-6.3]	<0.0001	5.3	[4.6-5.9]	NS	4.8 [4.0-5.6]	NS
ETP	102.7 [99.0-106.3]	162.6 [147.7-177.5]	<0.0001	174.2	[158.6-189.8]	<0.05	169.7 [153.3-186.0]	<0.05
Peak height	99.1 [92.7-105.5]	248.9 [223.4-274.5]	<0.0001	272.8	[244.0-301.6]	<0.05	267.1 [237.5-296.8]	NS
1 pM TF: difference after addition of TM (%)								
Lag time	-0.13 [-0.8-0.5]	1.0 [0.1-2.0]	<0.05	0.1	[-1.2-1.4]	-	0.2 [-0.7-1.1]	-
ETP	-42.2 [-44.0- -40.3]	-21.0 [-23.7- -18.3]	<0.0001	-18.8	[-21.4- -16.3]	-	-18.4 [-22.1- -14.7]	-
Peak height	-20.4 [-22.1- -18.7]	-3.1 [-4.7- -1.5]	<0.0001	-1.7	[-3.8-0.3]	-	-2.0 [-3.7- -0.3]	-

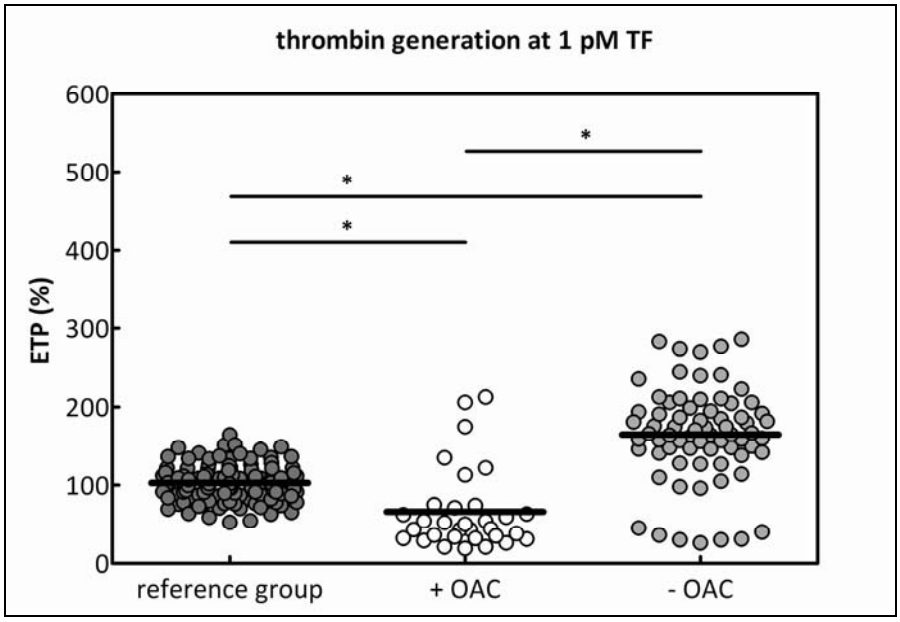
TF, tissue factor; ETP, endogenous thrombin potential; TM, thrombomodulin. Lag time is presented in minutes, ETP and peak height are presented as percentage of normal pooled plasma. HI, healthy individuals. B1=one month after cessation of anticoagulant treatment, B2=12 months after the event in patients without anticoagulant treatment, B3=24 months after the event in patients without anticoagulant treatment. Results from paired t-test between healthy individuals and patients at one month after cessation of treatment=P(B1-HI). Results from paired t-tests within patients=P(B2-1) and P(B3-1).

Initial CAT analyses were performed at 5 pM TF as indicated by the manufacturer. At these conditions patients without anticoagulant treatment showed significantly higher ETP at B2 and B3 and peak height at all time points compared to the reference ETP and peak height values. The lag times however did not differ significantly (Table 1). Furthermore, measurements of thrombin generation and peak height increased significantly over the course of one year and thereafter remaining sTable in the patient population without anticoagulant treatment; in the reference population thrombin generation and peak height did not change within the observed period of one year (data not shown).

The observed differences in ETP and peak height for patients after cessation of anticoagulant treatment and the entire reference population were even more

pronounced in assays triggered with 1 pM TF, suggesting an increased sensitivity compared to the 5 pM TF trigger.

Figure 1. Thrombin generation in the reference group and DVT patients. ETP is expressed as % compared to normal pooled plasma. Lines represent means.



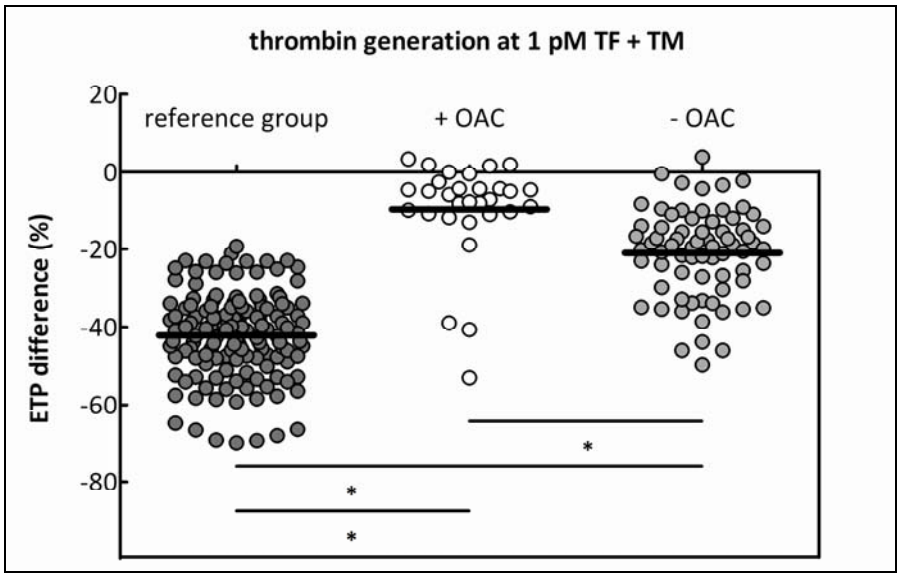
*+OAC, patients on vitamin K antagonists; –OAC, patients off vitamin K antagonists. * denotes P<0.05.*

As expected, at 1 pM TF the ETP of patients was significantly higher after cessation of anticoagulant treatment (-OAC) compared to the ETP in patients still on treatment (162.6 versus 65.8, P <0.0001). Patients on anticoagulant treatment (+OAC) showed decreased ETP also compared to those of a reference population (65.8 versus 102.7, P<0.0001; -36.9%). (Figure 1) Furthermore, patients on anticoagulant treatment had a prolonged lag time (9.9 versus 4.0 min, P < 0.0001; +147.5%) and a decreased peak height (109.8 versus 99.1, P < 0.0001; +10.8%) compared to the reference group.

We observed a marked reduction in the inhibitory potential of TM on the ETP in the patients off anticoagulant treatment as compared to the reference group (21% versus 42.2%, P<0.0001). (Table 1, Figure 2) The inhibition of ETP after addition of TM in patients on anticoagulant treatment (+OAC) was even less pronounced. (9.7%, P <0.0001). (Figure 2) We estimated that protein C activity

is responsible for 40% (R square 0.4) of the TM induced reduction in patients on anticoagulant treatment, while in patients without anticoagulant treatment this is only 20 %. The effect of TM remained unchanged after removal of the patients with a FV Leiden mutation (data not shown).

Figure 2. Difference in thrombin generation upon TM addition in the reference group and DVT patients. ETP is expressed as % compared to normal pooled plasma. Lines represent means.



*+OAC, patients on vitamin K antagonists; –OAC, patients off vitamin K antagonists. * denotes P<0.05.*

After addition of TM, protein C activity, protein S antigen and free protein S each showed a highly significant negative correlation with ETP in all patients both with and without anticoagulant treatment. Only after excluding patients diagnosed with a FV Leiden mutation, a significant negative correlation was found between FVIII levels and induced reduction of ETP and peak height by the addition of TM in our patient population. No significant differences were found in lag time in any of the groups (Table 2).

Table 2. *Correlations of TM reduction at 1 pM TF with FVIII, protein C (PC) activity, free protein S (PS) and total protein S. Data are presented as Pearson R.*

	FVIII	PC activity	free PS	total PS
reference range				
lag time TM difference	0.118	-0.198*	-0.247**	-0.060
ETP TM difference	0.171*	-0.354**	-0.515**	-0.267**
peak height TM difference	0.106	-0.346**	-0.465**	-0.186**
+ OAC				
lag time TM difference	0.057	0.012	-0.093	-0.062
ETP TM difference	-0.443*	-0.767**	-0.652**	-0.613**
peak height TM difference	-0.374	-0.332	-0.169	-0.179
- OAC				
lag time TM difference	-0.060	0.220	0.164	0.082
ETP TM difference	0.297*	-0.465**	-0.402**	-0.358**
peak height TM difference	0.244	-0.395**	-0.122	-0.114

** P < 0.01; ** P < 0.001.*

DISCUSSION

Our data show that thrombin generation is significantly higher in patients after recent DVT compared to thrombin generation in a reference population of healthy individuals. This elevation of the thrombin generating potential most likely reflects a hypercoagulable state in these patients.

This assumption is confirmed by our observations during follow-up. Thrombin generation varied in time in patients, while thrombin generation remained sTable in the reference population suggesting that levels of thrombin generation are related to the preceding thromboembolic event.

Relatively low ETP and peak height were found one month after cessation of anticoagulant treatment increasing to a significantly higher level after one year of follow-up. Although half-life times of coumarins lay between 48 and 72 hours, this phenomenon may be explained by a prolonged anticoagulant effect of the coumarins after cessation of treatment that is not yet established in other tests.

Secondly, we found more pronounced differences in thrombin generation responses between patients without anticoagulant treatment and the reference population after plasma stimulation with lower amounts of TF, 1 pM TF instead of 5 pM TF.

This effect is most likely caused by the increased sensitivity to subtle differences in endogenous plasma components at low TF stimulation as compared to the rather robust stimulation with 5 pM TF. At low TF concentrations, the interplay between mechanisms of activation and inhibition becomes more sensitive for the cofactor function of protein S in relation to tissue factor pathway inhibitor. [19]

In our study we furthermore observed that addition of TM lowers thrombin generation less efficiently in patients after a recent event of DVT as compared to thrombin generation in a reference population. This finding is in agreement with previously published work from Dargaud et al, who tested the effect of TM at the higher 5 pM TF concentration. [20] The lack of significant differences found in the lag time upon TM addition in any of the groups is obviously due to the fact that inhibition only takes place in the propagation phase after thrombin is activated.

Our data indicate that, as expected, proteins C and S are determinants of the effect of TM in all patients. Proteins C and S were contributing more strongly to the inhibition induced by TM in patients still on coumarin treatment. This can be explained by the fact that ETP is lowered by TM in an APC/protein S-dependent manner and since treatment with vitamin K antagonists lowers levels of active protein C and S [21], the residual protein C activity is rendered closer to the rate limiting amount of active protein C in these patients. The decrease in ETP following the addition of TM is therefore mainly dependent on the amount of residual protein C activity.

Finally we observed a significant negative correlation between FVIII levels and TM reduction in our patient population, after excluding patients diagnosed with a factor V Leiden mutation from the analysis. That the effect of TM remained unchanged after removal of the patients with a FV Leiden mutation does not imply that factor V is no determinant in TM induced inhibition of thrombin generation, but the contributory effect of factor V may be too small to be noted

at the test conditions used, where factor VIII may be a slightly dominant cofactor. The observed negative correlation between factor VIII and TM reduction can be explained by an enhanced feedback mechanism through thrombin dependent FVIII activation at increased levels of FVIII, thus counteracting the influence of TM on ETP and peak height (acquired APC-resistance). FVIII is not dependent on VKA treatment and is already known as a risk factor for recurrent DVT. [7, 8] The relation of FVIII with a reduced TM effect on ETP may explain some of the prothrombotic influence of elevated FVIII concentrations in relation to recurrent DVT.

The contributions of other endogenous determinants of this TM "resistance" remain to be established. We are aware of the limitations of our findings for as our patient group is a non selected heterogeneous group and comprises patients with various preexisting thrombosis risk factors (active malignancy, congestive heart failure, positive family history, previous episodes of VTE).

In conclusion, our findings show a clear difference in thrombin generation in patients following an acute episode of DVT as compared to a reference group of healthy individuals. This difference was most pronounced when the CAT was started with a low, 1 pM TF concentration. Hence, this lower TF concentration may be more suiTable to detect a hypercoagulable state in patients at risk of (recurrent) thrombosis. Thrombin generation with and without addition of TM provides information regarding several steps in the coagulation cascade including initiation and propagation. As demonstrated, FVIII is a determinant of reduced inhibition of thrombin generation after addition of TM and may explain part of the prothrombotic influence of elevated FVIII concentrations. The added information derived from an endogenous thrombin generation curve is that the overall rest capacity of thrombin generation, even under anticoagulant treatment, can be assessed.

This study was not performed to establish the clinical utility of the CAT assay. Future research should be aimed at unraveling the mechanism of impaired TM inhibition as a possible focus for improving management decisions regarding the duration of anticoagulant treatment in individual patients and ideally relate levels of endogenous thrombin generation over time to risk of recurrent thrombotic events.

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Chapter 11

High Levels Of Thrombin Generation In Relation To Increased Risk Of Recurrent Thrombosis

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ABSTRACT

Background: Recent studies suggest that thrombin generation (TG) may be able to distinguish between a low and a high risk for recurrence in patients

Objective: To study the possible relation between recurrent thrombosis and levels of TG, with and without thrombomodulin (TM), at different points in time between patients with and patients without a recurrent event.

Patients: 125 consecutive patients with confirmed proximal deep vein thrombosis (DVT) at the outpatient clinic of the academic hospital Maastricht, Maastricht, the Netherlands.

Methods: TG was determined under two experimental conditions (final plasma concentrations): 1 pM TF and 4 μM phospholipids in the absence and presence of 2 nM soluble TM. Differences between parameters of TG in the absence and presence of TM were analyzed between patients with and without a recurrent event. Furthermore, the association between TG and established risk indicators for VTE was assessed.

Results: Blood was obtained from 108 patients; 7 (5.6%) patients had an objectively documented recurrent event within the follow-up period. Significant differences were found between TG determined in the last sample before the recurrent event (PREC) compared to blood sampled one month after cessation of anticoagulant treatment (B1) as well as in samples at one year after the event (B2) in patients without a recurrent event. Upon addition of TM, the ETP showed a significantly reduced inhibition between patients with a recurrent event and those without a recurrent event (-9.0% versus -19.5%).

Significant associations were found between risk factors for VTE and TG. In particular lag time (LT) was associated with a number of variables that also determine risk of recurrent thrombosis, including residual thrombosis, previous thrombosis and age. FVLeiden and gender are of influence for ETP and PH. Upon addition of TM however none of the indices of TG are influenced anymore by known risk factors.

Conclusion: The assessment of TG in the presence of TM may therefore be practically useful. The observed change in TM responsiveness between patients with and those without recurrence may provide the opportunity to utilize this test to assess the risk in patients while still on anticoagulant therapy.

INTRODUCTION

The optimal duration of secondary prophylaxis for an acute thromboembolic process remains subject of research. Over the course of time many transient and permanent (genetic or acquired) risk factors have been identified. [2-10] The risk of a recurrent event lies around 3% per year for patients with a provoked event, 10% per year for idiopathic VTE, the 8 year cumulative incidence for recurrent VTE is about 30%. [11]

Currently, there are two major drawbacks to risk identification in patients after an acute event of venous thromboembolism (VTE). One is the inability to determine all risk factors present through the use of one single test. The other disadvantage is the uncertainty of the relative weight of each of the separate risk factors in the disturbance of the haemostatic balance. The quest for a global coagulation assay that reflects the balance between the pro and anticoagulant factors involved in the risk for (recurrent) thrombosis is therefore widely held.

It has been suggested that thrombin generation (TG) performed at one point in time is different between persons with and without an increased risk of a first episode of deep vein thrombosis (DVT). [12] A low chance of recurrence was found after acute DVT in patients with low endogenous thrombin potential (ETP). [13] More recently, high TG measured in the presence of thrombomodulin (TM) was associated with an increased risk of recurrent thrombosis. [14]

We previously documented that TG is not sTable in time but has relatively low values one month after cessation of anticoagulant therapy, and increases in the course of one year following the acute event of thrombosis. [Chapter 10] We were therefore interested to study the possible relation between levels of TG and recurrent thrombosis at different points in time after cessation of anticoagulant therapy.

We furthermore studied the influence of TM on TG in patients with as compared to those without recurrent thrombosis.

METHODS

Patients

Consecutive patients with confirmed proximal deep vein thrombosis (DVT) were followed for a period of 2 years after the acute event as part of routine patient care at the outpatient clinic of the academic hospital Maastricht, Maastricht, the Netherlands, between July 2003 and December 2006.

The study was approved by the local ethics board and written informed consent was obtained for additional blood collection in order to test thrombin generation. The inclusion of patients was consecutive and irrespective of the fact whether an event was a first event or a recurrent event and whether this event was idiopathic or provoked.

Anticoagulant treatment was installed according to international guidelines and was individually tailored when necessary. [15] Patients with provoked thrombosis were treated with anticoagulant medication for 3 months. Before cessation of therapy ultrasound examination of the afflicted leg was repeated to assess whether or not residual thrombosis was present. In case residual thrombosis was present, anticoagulant therapy was continued for another three months. [16]

For patients with a first event of idiopathic thrombosis initial anticoagulant therapy was installed for a period of six months. When residual thrombosis was found at ultrasound examination one week before planned cessation, patients would receive an additional six months of anticoagulant therapy.

Patients with previous events of venous thromboembolism were treated for at least 12 months or indefinitely.

Blood collection

Blood was drawn 1 month after cessation of treatment. In effect, blood was drawn at month 4 in patients with provoked thrombosis, and at month 7 in patients with idiopathic thrombosis (B1: 4-7 months).

The second round of laboratory tests was performed for the entire group off anticoagulant treatment at 12 months (B2), and the third at 24 months (B3).

Normal pooled plasma

Normal pooled plasma used for normalization of samples was prepared within the departments of Hematology and Clinical Chemistry of the University Hospital Maastricht, the Netherlands, by pooling plasma from 80-90 apparently healthy volunteers.

Blood collection and plasma preparation

Venous blood was collected in 3.2% citrate (w/v). Blood was drawn three times over the course of a two year follow-up period in all patients. Platelet poor plasma was prepared by two centrifugation steps: the first at 2000 g for 15 minutes and the second at 11000 g for 5 minutes, both at room temperature. Plasma aliquots were snap-frozen in liquid nitrogen, stored at -80°C until use. All samples were thawed at 37°C for 15 minutes before analysis and analyzed batch wise.

Thrombin generation measurements

Thrombin generation in tissue factor (TF)-triggered platelet poor plasma was measured by means of the Calibrated Automated Thrombogram (CAT) method (Thrombinoscope BV, Maastricht, the Netherlands), which makes use of a low affinity fluorogenic substrate for thrombin (Z-Gly-Gly-Arg-AMC) to continuously monitor thrombin activity in clotting plasma. In order to correct for inner-filter effects and substrate consumption, each thrombin generation measurement was calibrated against the fluorescence curve obtained in the same plasma with a fixed amount of thrombin-α_2-macroglobulin complex (Thrombin Calibrator, Thrombinoscope BV), as recommended by the manufacturer. Fluorescence was read in an Ascent Reader (Thermolabsystems OY, Helsinki, Finland) equipped with a 390/460 filter set, and thrombin generation curves were calculated with the Thrombinoscope software (Thrombinoscope BV).

Thrombin generation was determined under two experimental conditions (final plasma concentrations): 1 pM TF and 4 μM phospholipids in the absence and presence of 2 nM soluble thrombomodulin (TM). The TF triggers and phospholipids were obtained from Thrombinoscope BV; TM was kindly donated by Prof. Coen Hemker, Maastricht.

No corn trypsin inhibitor (CTI) to inhibit contact activation was included in our samples, although several authors reported reduced variability by means of contact factor inhibition using CTI. [17, 18] Contact activation was extensively assessed at previous occasions in our laboratory by analyzing TG in the absence of TF and was never observed in plasma obtained and prepared according to the described protocol (Spronk and van Oerle, unpublished data).

Three parameters were derived from the thrombin generation curves: lag time (LT), endogenous thrombin potential (ETP, area under the curve) and peak height (PH). Data for these parameters were normalized towards and given as ratio to normal pool plasma, analyzed on each plate, as described [Spronk et al, Thromb Haemostasis 2008; in press].

In order to test the inhibitory potential of the protein C pathway on thrombin generation TM was titrated to inhibit the ETP by approximately 50% in normal pooled plasma triggered with 1pM TF.

The FV Leiden mutation was determined with a commercial kit (Roche Diagnostics, Basel, Switzerland) on a Light Cycler instrument (Roche Diagnostics).

FVIII activity and APC resistance were performed on a CA7000 Coagulation instrument (Dade-Behring, Eschborn, Germany) according to the manufacturer's instruction. FVIII activity was measured with a one-stage clotting assay (Dade-Behring). APC resistance was measured with a Pro C AC R kit (Dade-Behring).

Statistical analysis

Descriptive statistics were computed for baseline characteristics, data are expressed as mean [95% confidence interval; CI 95%], unless otherwise specified. Descriptive statistics were computed for D-dimer levels and FVIII levels in the cohort for two different points in time, B1 and B2, data are expressed as mean (median). Difference between parameters of thrombin generation measurements (the 1 pM TF assay in the absence and presence of TM) within patients were analyzed with Student's t-test or Mann Whitney U as appropriate.

Differences between patients with and without recurrence were analyzed using paired Student's t-test or Wilcoxon signed rank test as appropriate. To test the association between TG and established risk indicators for VTE; LT, ETP and PH with and without TM were divided around the median of the cohort. Chi square was used to assess the following variables: previous VTE, varicositas/venous insufficiency, obesity (BMI>26), age over 70, gender, duration of anticoagulant therapy, residual thrombosis, levels of normal/abnormal D-dimer, levels of low/high FVIII, FVLeiden and malignancy. In the subsequent multivariate logistic regression analyses all variables that generated a p value of ≤0.05 on the Chi square test were entered.
A two-tailed probability value $P < 0.05$ was considered statistically significant. Statistics were computed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patients

All 125 patients who visited the outpatient clinic for the follow-up of an acute DVT consented to participate in the study and were included in the analysis. The baseline characteristics for these patients are shown in Table 1. The values of D-dimer levels and FVIII levels at two stages are presented in Table 2.

Clinical events

Of the 125 patients who were followed, complete follow-up was available for 102 patients; blood was obtained from 108 patients. 21 patients (16.8%) were lost to follow-up in the course of the two year follow-up period; 2 patients missed the visit at 6 months, 2 additional patients missed the 12 month visit, and 17 only missed the final visit. Of these 21 patients, 6 patients had moved away, 3 could not be followed due to substance abuse, 3 elderly patients had transportation difficulties, and one patient suffered a recurrent event and visited another hospital closer to her home while for the remaining 8 patients no particular reason for their lack of compliance could be identified.

Table 1. Patient characteristics.

Characteristics	n	(%)		
n=125				
Men; women	51	(40.8);	74	(59.2)
Age in years (SD; range)	55.8	(1.48; 17–82)		
BMI>26	65	(52)		
Risk factors VTE				
n=125				
Recent trauma ≤2 months	26	(20.8)		
Recent surgery ≤2 months	26	(20.8)		
Malignancy	5	(4.0)		
Hormonal therapy	26	(20.8)		
Pregnancy/puerperum	1	(0.8)		
FV Leiden (n=87)	21	(20.8)		
Varicositas/venous insufficiency	14	(11.2)		
Travel >10 hours	8	(6.4)		
Previous VTE	27	(21.6)		
Residual thrombosis	42	(35.6)		
Treatment duration				
n=125				
3 months	25	(20)		
6 months	61	(48.8)		
12 months	16	(12.8)		
24 months or indefinite	21	(16.8)		

BMI, body mass index; VTE, venous thromboembolism.

Recurrence and death

7 (5.6%) patients had an objectively documented recurrent event within the follow-up period; blood was obtained from 5 of these patients. In addition, 4 (3.2%) patients died during the follow-up period (2 male, 2 female; 3 of them died from metastasized malignancies (gastric, breast, lung) and there was one case of sudden death at home).

Analysis: TG and recurrent events

Differences between parameters of TG measurements (the 1 pM TF assay in the absence and presence of TM) between patients with and without recurrence are given in Table 2.

The first comparison was done between levels of LT, ETP and PH with and without TM, for patients with and without a recurrent event at one month after

cessation of anticoagulant treatment (B1). No statistical difference was found for any of the tested variables.

Table 2. Differences in thrombin generation, D-dimer and FVIII levels between patients with and without recurrent venous thromboembolism (VTE). Data are presented as median [interquartile range].

	No recurrent VTE (n=103)				Recurrent VTE (n=5)				P	P	P
	B1		B2		B1		PREC		(Prec-B1)	(Prec-B2)	(B1-B1)
FVIII (%)	184.5	[150.5-218.0]	181.0	[149.5-225.3]	171.5	[135.8-255.5]	187.0	[146.3-222.5]	NS	NS	NS
D-dimer (ng mL^{-1})	340.0	[125.0-510.0]	380.0	[242.5-665.0]	540.0	[212.5-770.0]	445.0	[210.0-1237.5]	NS	NS	NS
Thrombin generation 1 pM TF –TM											
Lag time (min)	5.0	[4.0-8.8]	5.0	[4.0-6.5]	5.6	[4.2-8.0]	4.0	[3.7-5.2]	NS	NS	NS
ETP (%)	148.0	[54.0-187.0]	171.0	[121.6-171.0]	148.0	[93.0-244.0]	212.0*†	[193.5-259.0]	0.027	0.027	NS
Peak height (%)	222.0	[100.0-303.0]	262.4	[144.5-323.0]	191.0	[104.0-427.5]	358.0*†	[310.0-464.0]	0.017	0.017	NS
Thrombin generation 1 pM TF +TM											
Lag time diff. (%)	0.0	[0.0-0.0]	0.0	[0.0-0.0]	0.0	[-0.90-3.78]	0.0	[0.0-0.0]	NS	NS	NS
ETP diff. (%)	-19.5	[-24.5- -17.5]	-16.0	[-25.2- -7.0]	-15.0	[-35.5- -10.5]	-9.0*	[-14.0- -5.5]	0.010	NS	NS
Peak height diff. (%)	-3.8	[-6.4- -2.2]	-26.9	[-34.9- -16.5]	-6.0	[-6.1- -2.7]	-25.2	[-33.2- -4.7]	NS	NS	NS

*PREC, last sample before recurrent event; diff., difference between thrombin generation in the presence (+TM) and absence (–TM) of thrombomodulin. * denotes P<0.05 compared to B1, † denotes P<0.05 compared to B2.*

When the same parameters were determined in the last sample before the recurrent event (PREC) as compared to blood sampled one month after cessation of anticoagulant treatment in patients without a recurrent event (B1), both ETP and PH were significantly different between patients with a recurrent event and those without.

Upon addition of TM, only the ETP showed a significantly reduced inhibition in patients with a recurrent event versus those without a recurrent event (-9.0% versus -19.5%).

Significant differences were found for both ETP and PH when levels of LT, ETP and PH with and without TM were compared for the last sample before the recurrent event (PREC) versus the sample at one year (B2) in patients without recurrence. When TM was added no significant differences were found.

TG and risk factors for VTE

The outcomes on the Chi square test for the association between LT and clinical risk factors, shows that LT is associated with residual thrombosis (p 0.001; OR

4.7 (1.8-12.2)), previous VTE (p 0.024; OR 3.8 (1.1-13.1)), estrogen use (p 0.005; OR 0.2 (0.06-0.6)) and age>70 (p 0.013; OR 3.0 (1.2-7.3)).
Patients with high ETP are more often female (p 0.043; OR 0.4 (0.2-0.9)), and have significantly less often FVLeiden mutation (p 0.013; OR 0.2 (0.05-0.7)) none of the other variables tested were significantly different.
Men have significantly lower PH (p 0.043; OR 0.4 (0.2-0.9)) as do patients with FVLeiden (p 0.013; OR 0.2 (0.05-0.8)).
In the subsequent multivariate logistic regression analysis of the variables associated with LT, estrogen use was not significant anymore, while residual thrombosis (0.004; OR 4.6 (1.6-12.9)), previous VTE (0.036; OR 4.6 (1.1-19.1)) and age >70 (0.046; OR 3.4(1.0-11.3)) were still associated. Both variables associated with ETP remained significant (0.041; OR 0.4(0.15-0.9)), (0.013; OR 0.2 (0.04-0.7)). For PH both gender (0.041; OR 0.4 (0.2-0.9)) and FVLeiden (0.013; OR 0.2(0.04-0.7) remained significant.
In the presence of TM, ETP and PH did not show any associations with risk factors for VTE. LT however, was associated with previous VTE (0.044; OR 4.7(0.9-23.4).
In the multivariate logistic regression analysis of the variables associated with LT in the presence of TM, none of the associations were present anymore.

DISCUSSION

The results of our study suggest that in general TG has the potential to be suiTable for global assessment of the risk of recurrent VTE in unselected patients.
In accordance with Tripodi et al. [14], our data show that levels of LT and ETP were not significantly different, in samples taken at one month after cessation of anticoagulant therapy between patients with and without a recurrent event. In disagreement with the results of the before mentioned study, we observed no differences in PH. Upon addition of TM we did not observe differences between TG of patients with and patients without a recurrent event. This may be due to the small number of recurrent events available for testing.
Timing of blood collection with regard to the optimal usefulness of the assay may be more important than currently appreciated. Closer towards the recurrent

event the potential to detect a procoagulant effect may be increased. This was manifested when the last measurements available before the recurrent event were compared to the samples of one month after cessation of therapy in patients without a recurrent event. Statistically significant differences in TG indices were observed. This was also the case for comparison to samples from patients without a recurrent event taken at a later point in time after cessation of anticoagulant therapy.

The fact that no statistically significant differences were found at one month after cessation of anticoagulant medication may, besides the lack of power, also be attributed to the relatively low levels of TG at that point in time compared to the significantly higher levels of TG at one year after the event. [Chapter 10]

It is furthermore of interest that associations were found between risk factors for VTE and TG. In particular LT was associated with a number of variables that also determine risk of recurrent thrombosis, including residual thrombosis, previous thrombosis and age. FVLeiden and gender are of influence for ETP and PH. Upon addition of TM however none of the indices of TG are influenced anymore by known risk factors.

The best practical usefulness for TG lies therefore in the assessment of TG in the presence of TM. We have shown earlier that under anticoagulant therapy inhibition with TM is significantly different in patients as opposed to healthy individuals. [Chapter 10] It would be interesting to study whether TM has different levels of inhibition during anticoagulant therapy between patients with a recurrent event and patients without. The most attractive management strategy may be to test the inhibitory potential of TG at different points in time during anticoagulant treatment.

Finally, it must be stressed that the character of this study is exploratory and that given the few events observed, no firm conclusions can be drawn as of yet. In spite of such limitations the present data provide important new information regarding the dynamics of the pre-thrombotic state. This may add to improved diagnostic options in patients at risk of recurrent DVT.

In addition, and in accordance with the data from Tripodi and colleagues, the observed change in TM responsiveness between patients with versus those

without recurrence may provide the opportunity to utilize this test to assess the risk in patients while still on anticoagulant therapy.

Further studies are needed to assess the optimal point in time for determination of the risk of recurrence and in order to derive the mechanisms involved in the changes in TG towards the time of the recurrent thrombotic event.

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Chapter 12

Individually tailored duration of elastic compression therapy in relation to incidence of the Post Thrombotic Syndrome

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Submitted

ABSTRACT

Background: Current guidelines for prevention of post thrombotic syndrome (PTS) after an acute deep vein thrombosis (DVT) are to wear elastic compression stockings for a period of 2 years. However, the optimal duration of therapy for individual patients is uncertain.

Objective: To assess whether individualized shortened duration of elastic compression therapy of at least 6 months after an acute DVT lead to an accepTable incidence of PTS.

Patients: 125 consecutive patients with confirmed proximal DVT were followed for 2 year at the outpatient clinic of the university hospital Maastricht.

Interventions: On 4 consecutive visits (3, 6, 12 and 24 months after the acute event) clinical signs and symptoms were scored according to Prandoni. Compliance of elastic compression therapy was recorded. Reflux was objectivated by duplex ultrasound testing. Patients with scores ≤ 4 on Prandoni in the absence of reflux were advised to discontinue compression therapy. Patients with reflux and stabile scores ≤ 4 were also allowed to stop compression therapy in the course of the follow-up.

Results: Of the patients with scores ≤ 4, 17% stopped compression at 6 months, 48% at 12 months and 50% at 24 months. Duplex ultrasound testing was done in 101(80.8%) of patients; 74 patients had reflux, 40 stopped wearing elastic compression stockings. Of these patients 31(77, 5%) had a low PTS score and 9(22, 5%) had a high PTS score. At six months the cumulative incidence of PTS was 13.2%, at 12 months 17.6% and at the 24 month visit 22.4%. At multivariate regression analysis only varicositas/venous insufficiency at baseline remained significantly associated with PTS (OR 4.7 (1.1-19.7).

Conclusion: Individualized duration of compression therapy based on clinical score and results on reflux testing is unlikely to have a negative impact on the incidence of PTS. The presence of varicositas/venous insufficiency ay baseline may make patients more susceptible to PTS.

INTRODUCTION

Post Thrombotic Syndrome (PTS) is a chronic condition that arises in 20-50% of patients following Deep Vein Thrombosis (DVT) and is therefore considered to be the most common complication of DVT. [1-4] The syndrome not only reduces the quality of life of those afflicted [5] but also generates substantial healthcare costs. [6]

Post thrombotic complaints secondary to acute DVT are due to venous hypertension caused by venous obstruction or valve destruction. Venous hypertension results in reduced calf muscle perfusion, increased tissue permeability and clinical symptoms typical of PTS. The clinical manifestations of PTS are: pain, edema, skin changes, venous claudication and in severe cases even venous ulcers may occur.

The obstruction of post thrombotic limbs by residual thrombosis is considered to be the main cause of complaints [7-9] Moreover, the presence of reflux in the femoral vein and popliteal vein after an event of DVT is thought to contribute to the development of PTS. [10] The highest levels of ambulatory venous pressure occur in patients with combined outflow obstruction and distal reflux.

However, patients may have valvular incompetence after DVT but at the same time not suffer from PTS. [11, 12] The clinical diagnosis of PTS is based on clinical signs and symptoms that are scored according to a clinical scale. [13-15] Duplex ultrasound ultrasound is predominantly used for objective confirmation of the diagnosis of PTS. In the absence of clinical symptoms the diagnosis PTS must not be made.

Occluded vein segments usually recanalize within 6 -12 months. After 12 months complete re-canalization is obtained in only 50% of cases. [16] Significantly more re-canalization is found with early compression. [17-19] In most cases however only partial clearance of thrombus occurs. [20, 21] There is no unambiguous evidence yet for the reduction in the risk for PTS after clot lysis as compared to standard anticoagulation therapy. [22, 23]

Risk factors for development of PTS have been investigated extensively. The strongest risk factor appears to be ipsilateral recurrent DVT. [1, 24, 25] Elevated D-dimer levels (>500 ng/ml) after cessation of anticoagulant medication are considered a modest risk factor for PTS [3] as is a high body

mass index (BMI). Factor V Leiden mutation is found to be an independent predictor of lower risk of PTS in patients with idiopathic DVT [26] ,adequate anticoagulation in the first months after DVT may also diminish the risk of developing PTS. [25] No association is found between residual thrombosis and PTS [26, 27], the duration of anticoagulant treatment [3], thrombophilia in general [1, 25, 26] and age or sex in relation to the occurrence of PTS. [24, 25, 5, 3] The majority of cases of PTS occur within 1 year of the DVT. Elastic compression therapy has been observed to reduce the incidence of PTS in unselected patients by almost half. [1] Compression therapy reduces venous reflux [28-30] and improves calf muscle pump function. Furthermore enhancement of the circulation of the skin and subcutaneous tissue are assumed in addition to effects on subcutaneous pressure. [13]

The evidence sustaining the value of compression therapy after an acute event of DVT in order to reduce the incidence of PTS is derived from 4 randomized clinical studies. [17, 24, 31, 32], In these trials however no selection was made or assessment was done to evaluate whether some patients could benefit more from prolonged therapy than others.

Therefore the issue whether all patients need to have prolonged compression therapy for a period of two years remains unsolved. Compliance with therapy can be demanding for all patients, but this could possibly be even more the case for patients who do not have any complaints.

In a prospective cohort study we therefore assessed (based on clinical PTS score and the result on duplex ultrasound analysis) whether individualized shortened duration of elastic compression therapy after initial compression therapy of 6 months following an acute event of DVT has a negative impact on the incidence of PTS. In addition we evaluated whether some of the known risk factors for PTS can help in the selection of patients who can potentially benefit more from prolonged compression therapy.

METHODS

Patients

Consecutive patients with confirmed proximal DVT were followed for a period of 2 years after the acute event as part of routine patient care at the

outpatient clinic of the academic hospital Maastricht, Maastricht, the Netherlands, between July 2003 and December 2006. At the first visit patients were informed about the use of their clinical data and informed consent was obtained. This evaluation was part of another study that was approved by the institutional review board.

Anticoagulant treatment was installed according to international guidelines and individually tailored when necessary. [34] Patients with provoked thrombosis were treated with anticoagulant medication for 3 months. Before cessation of therapy ultrasound examination of the afflicted leg was repeated to assess whether or not residual thrombosis was present. In case residual thrombosis was present, anticoagulant therapy was continued for another three months.

For patients with a first event of idiopathic thrombosis initial anticoagulant therapy was installed for a period of six months, when residual thrombosis was found at ultrasound examination one week before planned cessation, patients would receive an additional six months of anticoagulant therapy.

Patients with previous events of venous thromboembolism were treated for at least 12 months or indefinitely.

Baseline examination

At the screening visit a thorough medical check up was performed and a clinical history was taken. Risk factors were assessed both for VTE and for PTS. Risk factors for PTS included: previous VTE, presence of malignant disease, obesity, age over 70 years, known thrombophilic defects and history of varicose veins or venous insufficiency

Elastic compression therapy

All patients were initially bandaged for as long as it took for the acute edema to resorb; afterwards elastic compression stockings were custom fitted and patients were advised to wear these stockings during the daytime. The stockings prescribed were flat knitted stockings in two parts, one part for the upper section of the leg from thigh to knee, the other part was a knee length stocking. A class III pressure was standard. For elderly patients and patients with arterial insufficiency a class II stocking was stipulated. (Mediven ®550, ankle pressure 40 mmHg (Class III) or 30 mmHg (class II)) All patients were advised to wear

elastic compression stockings for a minimal duration of six months after the acute event, the upper part of the stocking was worn for no longer than 6 weeks.

Assessments

Patients visited the outpatient clinic 5 times following the acute event. The first visit took place within a month of the event, the second visit at 3 months after the event, the third at 6 months, the fourth at 12 months and the final visit at 24 months after the event.

All 125 patients who visited the outpatient clinic for the follow-up of an acute deep vein thrombosis were assessed at each of the 4 follow-up visits, following the initial screening visit, for compliance of elastic compression therapy. At each visit a clinical assessment of the afflicted leg was performed and signs and symptoms were scored using the Prandoni score. In addition Duplex ultrasound analysis was performed.

Assessment of post thrombotic syndrome

The presence of signs and symptoms indicative of post thrombotic syndrome were scored according to the Prandoni score. [38] This score contains 5 leg symptoms and 6 objective signs. The leg symptoms comprise: pain, cramps, heaviness, pruritis and paresthesia. The objective signs are: pretibial edema, induration, new venous ectasia, redness and pain during calf compression. For all items separately a score of 0 to 3 could be assigned. Patients were classified as having post thrombotic syndrome if they had a score of ≥5 or more on 2 or more consecutive visits that where at least 3 months apart. Venous ulceration classified as severe post thrombotic syndrome regardless of the sum score total. [1] All patients were scored by one physician during the entire follow-up period.

Duplex ultrasound assessment

Patients were examined in a standing position on a tilting Table in a 45° angle. Proximal reflux was measured after the Valsalva maneuver; distal reflux was measured by manual compression with sudden release. Normal duration of reflux in proximal veins was less than 1.0 seconds, in a distal vein less than 0.5 seconds. The scanner type used was Aloka SSD-2000, the probe type used a 7.5

MHZ linear transducer (for deep veins a 3.5 MHZ transducer was used) at low flow setting.

Patient management

Based on absence of complaints (Prandoni score ≤ 4) and absence of reflux on duplex ultrasound testing, patients were allowed to discontinue elastic compression therapy.

Patients were advised to continue compression therapy in case a PTS score of ≥5 was present and or if reflux was found. In case PTS scores improved in patients with objectivated reflux in the course of the follow-up patients were allowed to stop compression therapy.

Patients were considered to suffer from PTS if they had a score of ≥5 on two separate occasions at least 3 months apart.

Analysis

Descriptive statistics were computed for baseline characteristics and PTS scores per visit in relation to compression therapy.

Cumulative incidences of the post thrombotic syndrome were calculated in the actuarial method.

The association between PTS and clinical characteristics was assessed for categorical variables using the Chi square test. The variables analyzed were: risk factors for PTS such as: previous VTE, varicositas/venous insufficiency, obesity (BMI>26), age over 70, gender, duration of anticoagulant therapy, residual thrombosis, reflux, known thrombophilic defects and malignancy.

In the subsequent multivariate logistic regression analysis all variables that generated a p value of ≤0.05 on the Chi square test were entered.

All analyses were performed with SPSS software package 13.0 for Mircosoft Windows.

RESULTS

Patients

All 125 patients who visited the outpatient clinic for the follow-up of an acute deep vein thrombosis were included in the analysis. The baseline characteristics for these patients are shown in Table 1.

***Table 1**. Characteristics of study population (n=125)*

Characteristics	N (%)
Men/women	51 (40.8)/74(59.2)
Age in years	55.8 SD 1.48 (17-82)
BMI>26	65 (52)
Risk factors VTE	
Recent trauma	26 (20.8)
Recent surgery	26 (20.8)
Malignancy	5(4.0)
Hormonal therapy	26(20.8)
Pregnancy/puerpurum	1(0.8)
Known thrombophilia	7 (5.6)
Varicositas/venous insuff.	14 (11.2)
Travel>10 hours	8(6.4)
Previous VTE	27 (21.6)
Treatment duration	
3 months	25 (20)
6 months	61 (48.8)
12 months	16 (12.8)
24 months or indefinite	21 (16.8)

Clinical events

Of the 125 patients who were followed, complete follow-up was available for 102 patients. 21 patients (16.8%) were lost to follow-up in the course of the two year follow-up period; 2 patients missed the visit at 6 months, 2 additional patients missed the 12 month visit ,and 17 only missed the final visit. Of these 21 patients, 6 patients had moved away, 3 could not be followed due to substance abuse, 3 elderly patients had transportation difficulties, and one patient suffered a recurrent event and visited another hospital closer to her home while for the remaining 8 patients no particular reason for their lack of compliance could be identified.

Recurrence and death

7(5.6%) patients had an objectively documented recurrent event within the follow-up period. In addition 4 (3.2%) patients died during the follow-up period (2 male, 2 female; 3 of them died from metastasized malignancies (gastric, breast, lung) and there was one case of sudden death at home.

Post thrombotic complaints and syndrome

Overall 39 (31.2%) patients had a Prandoni score of ≥5 on any of the 4 visits. Based on the definition of the Post thrombotic Syndrome, a score of ≥5 on two separate occasions at least 3 months apart, only 25 (20%) of the 125 patients developed the Syndrome in the course of the two year follow-up period. Three of these patients had severe PTS; one was diagnosed with and treated for a venous ulcer at another hospital.

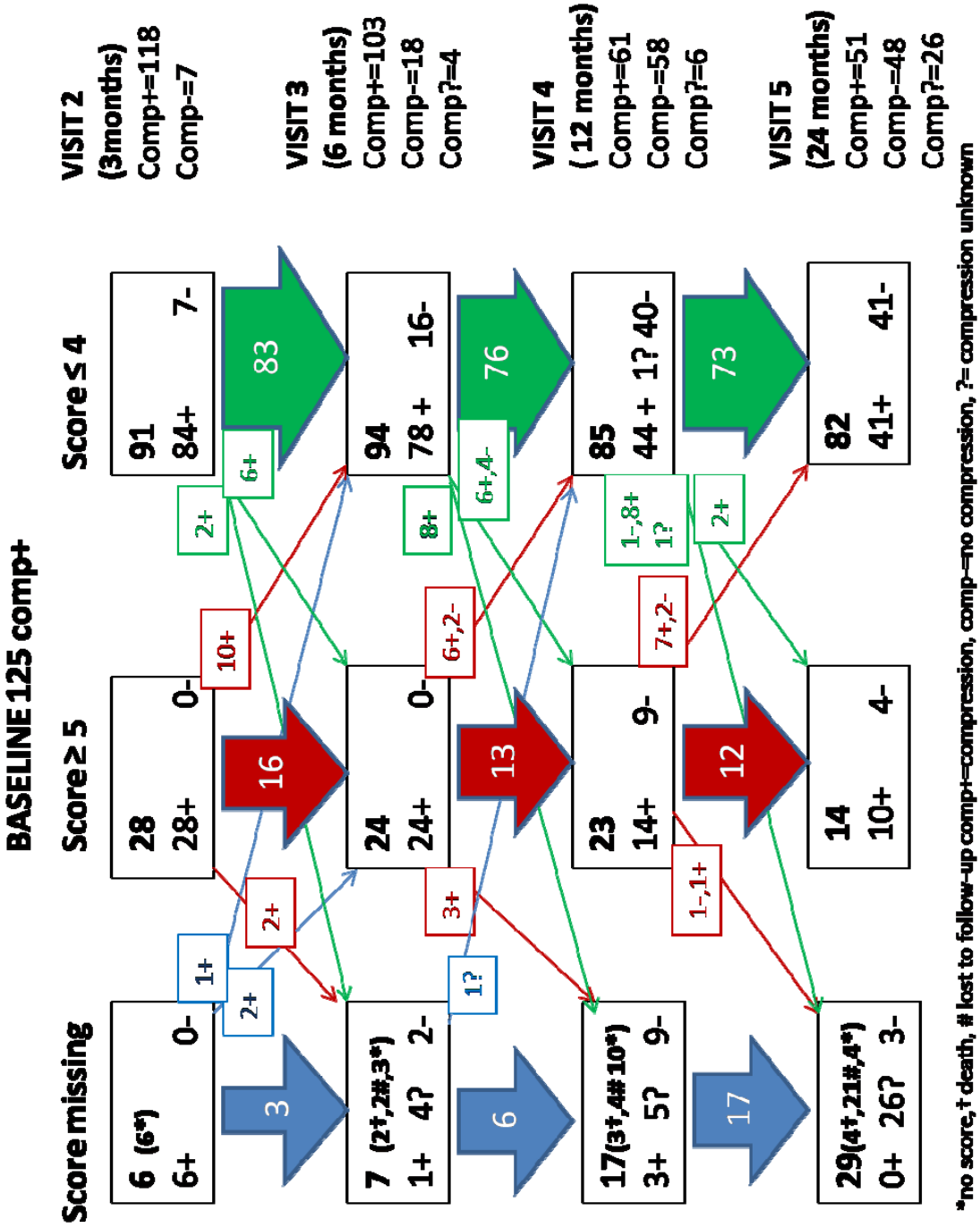
The results of the dichotomized Prandoni score in all patients as well as the transitions between the high and low score group for each of the visits are presented in Figure 1.

It is interesting to note that many patients with initially one or two scores above the threshold of 5, cross over to the low score group at later visits. Of the 29 patients that are not included in the final assessment, 7 (5.6%) had a high score at the last assessment and 20(16%) had a low score at the last assessment, 2 had an unknown score from the start.

Of the patients who were once diagnosed with PTS overall 9 patients improved, 4 of the patients initially diagnosed with symptomatic PTS did not have complaints anymore over the course of the first year and an additional 5 patients were free of complaints at month 24. Only 2 patients worsened after cessation of elastic stocking therapy

At 6 months after the event, 16 patients met the criteria for the diagnosis of PTS. At 12 months, one patient improved and an additional 5 patients were newly diagnosed with PTS, resulting in 17 patients with symptomatic PTS. After 24 months an additional 4 patients were diagnosed while at the same time 5 patients improved leading to a total of 18 patients with symptomatic PTS at visit 5.

At 6 months the cumulative incidence of PTS was 13.2%, at 12 months 17.6% and at the 24 month visit 22.4%.


BASELINE 125 comp+
Score missing
Score ≥ 5
Score ≤ 4
VISIT 2 (3months) Comp+=118 Comp-=7
VISIT 3 (6 months) Comp+=103 Comp-=18 Comp?=4
VISIT 4 (12 months) Comp+=61 Comp-=58 Comp?=6
VISIT 5 (24 months) Comp+=51 Comp-=48 Comp?=26
6 (6*) 0-
6+
28 28+
91 84+ 7-
7 (2†,2#,3*) 2-
1+ 4? 1?
24 24+ 0-
94 78 + 16-
17(3†,4# 10*) 9-
3+ 5?
23 14+ 9-
85 44 + 1? 40-
29(4†,21#,4*) 3-
0+ 26?
14 10+ 4-
82 41+ 41-
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6+
3+
6+,2-
1?
8+
6+,4-
1-,1+
7+,2-
1-,8+ 1?
2+
*no score,† death, # lost to follow-up comp+=compression, comp-=no compression, ?= compression unknown

Figure 1. *Transition of patients between low and high scores for each visit. Orange vectors = patients with missing score, red vectors = score ≥5, green vectors = score≤4. Orange arrow= transition of patients with missing score, red arrow= transition of patients with a score ≥5, green arrow= transition of patients with a score ≤4. *no score available, †death, # lost to follow-up, comp+= with elastic compression, comp-= without elastic compression, ? =status of compression unknown.*

Use of elastic compression stockings

Patients with Prandoni scores ≥5 were all wearing stockings for at least 6 months, at one year 60.9% had compression therapy and at the two year follow-up visit 71.4% of these patients were wearing elastic compression stockings.

Patients with Prandoni scores ≤4 stopped wearing compression stockings as early as 3 months (7 patients stopped on their own account), at 6 months 17% did not wear stockings, at 12 months 48% and at the two year follow-up visit 50% did not have elastic compression any more.

The 7 patients, who stopped elastic compression on their own account, developed no PTS. Of the patients who stopped compression therapy based on a low clinical score, 5 patients re-started compression therapy because of worsening of symptoms. These patients although they did discontinue compression for some time did not develop PTS.

Interestingly, half of the patients with a low Prandoni score remained wearing their elastic compression stockings, mainly because they thus experienced more comfort.

Duplex ultrasound testing

Duplex ultrasound testing for reflux was done in 101(80.8%) patients, a total of 74 (73.3%) had reflux either in the superficial veins or in the deep venous system or both. Thirty one (31%) patients in whom reflux was objectivated in the deep vein system had repeated duplex testing; no improvement was seen on repeated duplex ultrasound testing over time. Over the course of the total follow-up period from the 74 patients with reflux, 40 stopped wearing elastic compression. 31(77.5%) patients with a low PTS score and 9 (22.5%) patients with a high PTS score.

Risk factors for the Post thrombotic Syndrome

Of the tested variables, reflux, varicositas/venous insufficiency and anticoagulant therapy of 3 months were significantly associated with post thrombotic syndrome in the univariate analysis. Duration of anticoagulant treatment of 3 months had a negative association with PTS; p=0.025, OR 0.1(0.02-0.8)), varicositas/venous insufficiency had a positive association; p=<0.001, OR 7.1 (2.3-22.1) as well as reflux on duplex ultrasound; p=0.024, OR 7.9 (1.3-48.4).

At multivariate logistic regression analysis however only the association with varicositas/venous insufficiency remained significant; p=0.035, OR 4.7(1.1-19.7) and previous episodes of VTE, age over 70, gender, residual thrombosis, and longer duration of anticoagulant therapy, malignancy, reflux and obesity were not associated with PTS.

DISCUSSION

The outcomes of our study show that individualized duration of compression therapy results in a cumulative incidence of PTS of 22.4%. This compares well with results of active randomized studies. [17,24]. Hence, it seems that tailoring the use of elastic compression therapy based on a clinical score and results on duplex analysis has no negative impact on the incidence of PTS.

The patients with low scores for PTS who do not develop PTS form a stabile group. Patients with a higher score are more versatile, half of these patients have variable high and low scores at each visit. Patients with severe PTS however can already be identified at the 6 month visit. Only a very small proportion of patients (2%) get worse after one year.

There are sound arguments for sustaining compression therapy for at least 6 months in all patients. Firstly, thrombus regression takes approximately 6-12 months and earlier studies have shown that thrombus regression can benefit from compression therapy. Secondly, the appraisal of patients in the sub-acute stadium of DVT can be difficult because of complaints related to the acute phase of the thrombosis. Finally, the diagnosis PTS can only be made when the score is ≥5 on two consecutive occasions that are at least 3 months apart.

From our observations however we have learned, that patients with a low clinical score who experienced worsening of symptoms after discontinuation of compression therapy did not develop PTS although they did suspend compression for some time. To stop compression therapy on a trial bases could therefore be considered as a management option.

On the other hand we observed that a considerable proportion of patients with no complaints and low clinical scores voluntarily continued compression therapy because they thought it was more comforTable.

In our cohort we have evaluated some of the risk factors mentioned in the literature and in addition also looked at varicose veins/venous insufficiency as a possible risk factor. Although reflux as well as residual thrombosis is considered to be causative for venous hypertension no association with PTS with any of these two factors has previously been found.

We found that reflux on duplex ultrasound had a positive association with PTS but only when deep as well as superficial reflux was considered. Deep reflux alone was not significantly associated. Short duration of anticoagulant treatment had a negative association with PTS. The strongest association however was found between PTS and varicositas/venous insufficiency. This association remained significant after correction for other possible risk factors.

Varicositas/Venous insufficiency has been previously associated with an increased risk of DVT; it might be possible that one common factor plays a role in these two disease presentations. We based management on clinical score and reflux, these observations suggest that varicositas/venous insufficiency at initial presentation can also be used to make a selection between a low and a high risk for developing PTS.

Up until now it is still unclear what the actual mechanism of the effectiveness of initial compression therapy consists of. Swift thrombolysis may not be the main accomplishment since no associations have been found between residual thrombosis and PTS. An adequate initial anticoagulation therapy however has been associated with reduced incidence of PTS. Maybe it is not the so much the obstruction of the vein by thrombus material that induces PTS but the thrombolytic activity of enzymes and the thus induced damage. Better initial anticoagulation therapy could result in a reduced thrombus burden and therefore

reduced thrombolytic activity. Early compression improves circulation of the skin and subcutaneous tissue and may contribute by adequate removal of products of thrombolytic enzymes.

The presence of varicose veins or venous insufficiency could have a negative impact on enzyme clearance and thus make these patients more susceptible for PTS. These patients may benefit from interventions directed towards an incompetent superficial venous system. [36] Ligation, stripping as well as foam sclerotherapy can be employed even in the presence of co-existent deep reflux. [37]

IN CONCLUSION

The success of elastic compression therapy is mainly due to the initial therapy phase. It is still unclear what the mechanism of this initial therapy is and whether this phase should comprise 3 or 6 months after the acute DVT.

For the majority of patients elastic compression therapy with duration of 6 months is sufficient. There is only a small group of patients who have a predisposition for PTS; they will develop PTS regardless of elastic compression therapy.

Elastic compression therapy is mainly useful as a preventive measure. For the small group of patients who develop PTS more effective treatment options should be established [38-42].

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Chapter 13

GENERAL DISCUSSION

INTRODUCTION

The main objectives of this thesis were to evaluate the current diagnostic procedures and therapeutic options for Deep Vein Thrombosis (DVT). To address these general objectives, a literature review, a large prospective management study and three sub-studies have been performed concerning the diagnostic procedures. In addition two literature reviews and two studies, one clinical study and one laboratory study, have been performed regarding the therapeutic options. Since the amount of information that is generated in the field of thrombosis by clinical studies as well as laboratory studies, review studies of the literature were done in order to assess the state of the art situation for both subjects. This chapter gives a summary of the main findings. In addition some recommendations for future research are given.

MAIN FINDINGS

PART ONE

An overview of Systematic Reviews

The objective of this overview was to systematically address all relevant features of a systematic review and to acknowledge the usefulness of reviews in modern evidence based medicine.

Systematic reviews are essential for informed health care decisions and should be based on a clear clinical question. Systematic reviews are considered the highest quality of evidence. Nevertheless, the strength of the conclusion can be weak, even if the review is conducted according to the highest standard of quality. The underlying quality and consistency of the evidence included in a systematic review therefore is crucial. [1, 2]

PART TWO

Management studies using a combination of D-dimer test result and clinical probability to rule out venous thromboembolism; a systematic review

A systematic review was conducted assessing the safety and the decrease in need for diagnostic imaging of strategies in which a combination of a Clinical Decision Rule (CDR) together with a D-dimer assay result was used to exclude venous thromboembolism in patients with a negative D-dimer and a low clinical probability. The primary outcome measure was the incidence of objectively confirmed symptomatic venous thromboembolism (VTE) over a period of 3 months among these patients.

The main research question was whether based on the synthesized knowledge extracted from clinical trials addressing this issue; a clear conclusion regarding this procedure could be formulated.

The results of this review indicated that it can be concluded that withholding anticoagulant treatment in patients suspected of VTE on the basis of a work-up consisting of a CDR and a D-dimer test result, is safe for the group of patients with a normal D-dimer test result and a low clinical pretest probability score. [3-13]
No statistically significant difference in safety profile was found between quantitative and qualitative D-dimer tests. This implies that the primary assessment of patients can be transferred to an out of hospital setting using qualitative D-dimer tests or point-of-care D-dimer tests. [14]

Safely ruling out deep venous thrombosis in primary care
A cohort study was conducted in primary care in the Netherlands (AMUSE study) in which approximately 300 general practitioners participated. Consecutive patients presenting with clinically suspected deep vein thrombosis (DVT) based on the presence of at least one of the following symptoms; swelling, redness or pain of the lower extremity were eligible for the study. Patients had to be over 18 years of age and not on anticoagulant treatment.

Our main research question was whether patients suspected of DVT in primary care can be safely excluded from ultrasound examination and withheld

anticoagulant treatment based on a decision rule including a clinical score and a point of care D-dimer test.
A second research question was whether or not this approach was feasible in the primary care setting.

The findings of this study indicated that the considered approach was not only safe but also efficient, since the need for referral was reduced by almost 50%, at the cost of an accepTable low risk of subsequent thromboembolic events (1.4% 95 CI 0.6-2.9) in the non-referred patients. Also in relation to feasibility the outcomes were positive, since 97% of patients could be managed based on the diagnostic strategy.

Optimization of the diagnostic strategy for suspected deep vein thrombosis in primary care

We analyzed the data of the AMUSE study. To test whether the accuracy of the used diagnostic algorithm could be improved we applied updating methods to the existing rule, using the data collected in the AMUSE study. [15-18]

We investigated whether the accuracy of the diagnostic strategy used in the management study could be further improved by adjusting the weights of the included predictors or by adding new diagnostic predictors.

The weight of the individual predictors in the rule did not need adjusting. Significant predictive value was added by including "history of DVT" and "prolonged travel" to the rule, this had however no clinical relevant effect. At equal safety (1.4% missed diagnoses in non-referred patients) lower efficiency was achieved (43.5% compared to 49%).
Furthermore, an adapted strategy was proposed for patients with a high clinical score (15% of patients) because the risk of DVT is still high when the D-dimer test is normal (23.6%). The conclusion was that these patients should be referred to hospital for ultrasound examination regardless of their D-dimer level.

Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual

For this study a Markov model was constructed, in order to estimate the expected quality-adjusted survival duration and life time costs for the cohort. We simulated the course of events in a hypothetical cohort similar to the cohort studied in the Amuse study. The cycle length of the model was set to 6 months, with a 5 year time horizon. The model was constructed to compare the expected 5-year costs and health effects of different diagnostic strategies for suspected DVT. [19]

We assessed whether the amuse strategy was cost-effective as compared to usual care based on either ultrasound alone or on ultrasound following an in-hospital rule.

Three diagnostic strategies were compared; probabilities were derived from the Amuse study and the literature. The Amuse strategy had both slightly lower costs and less QALY than both other strategies. This resulted in a saving of 138€ and a very slight QALY loss (0.002). The ICER was 56.436€. Cost-effectiveness acceptability curves showed that the Amuse strategy had the highest probability of being cost effective, even when ceiling ratio's exceed 80.000 €.

These findings indicate that from a societal perspective it seems cost-effective to implement the Amuse strategy.

Common alternative diagnoses after exclusion of DVT in symptomatic patients in general practice.

The majority of patients who are initially suspected of deep vein thrombosis are eventually assigned an alternative diagnosis. Not much is known about the clinical fate of these patients.

We therefore have addressed this lack of information by studying the following questions: what do the common alternative diagnosis consist of in general practice, is it possible to differentiate between these alternatives using certain

signs and symptoms, can a risk assessment strategy have added value, what treatment strategies are adopted and finally what happens to these patients in a three month follow-up period.

We found that alternative diagnoses in primary care differ from those in secondary care and that the most prevalent working diagnoses were: muscle rupture, chronic venous insufficiency, erysipelas/ cellulitis and superficial thrombophlebitis. Diagnoses were mainly based on clinical symptoms, and risk assessment strategies were only helpful when the score was low, the most common policy followed was an expectative policy (30% of cases). For the majority of patients an expectative policy was sufficient. Closer surveillance may be required in case of the alternative diagnosis SVT, since we found that DVT was more prevalent in these patients in our cohort.

PART THREE

Appropriate level and length of post-thrombotic warfarin treatment; an evaluation of recent developments

A narrative review was conducted; studies on therapy intensity as well as studies on therapy duration were reviewed. Additionally studies considering the different qualities of vitamin K antagonists (VKA) and low molecular weight heparins (LMWH) for different groups of patients and studies evaluating the issue of individualization of duration of anticoagulant treatment were described. Only very limited data on new anticoagulant medication was evaluated.

The main objective of this review was to assess the current knowledge about the level as well as the duration of warfarin treatment following an event of DVT.

When VKA's are used for treatment of thromboembolism the dose should be adjusted to maintain an INR between 2.0 and 3.0. [20-22] Lower intensities are less effective and not proven to be safer, while higher intensities are equally effective but cause more bleeding.

After cessation of anticoagulant therapy the risk of recurrence varies between 3% per year in patients with a first episode of VTE, associated with a transient

risk factor [23] and at least 10% per year, in patients without reversible risk factors as well as in patients with cancer. [24] Up until today the optimal duration of anticoagulant treatment remains a subject of debate [25], mainly due to the inability to account for all individual risk factors for recurrent thromboembolism.

VKA therapy is less effective and associated with an increased risk of recurrence during treatment for patients with underlying cancer. [26] Despite adequate treatment, recurrent events, bleeding and death are more common in this population. [26-28] LMWH proves to be a better option than a vitamin K antagonist for patients with cancer.

The future position of VKA therapy will be challenged and therapy recommendations will change due to the development of new agents.

Low molecular weight heparins in cancer

A second narrative review was undertaken to clarify the position of LMWH's in the management and prevention of VTE in patients with malignancies.

Mechanisms

Tumor cells have the ability to activate blood coagulation. Tissue Factor (TF), thrombin, fibrin and proteins that regulate the fibrinolysis (urokinase, plasminogen) are directly involved in tumor growth and dissemination. [29] The anti tumor effects of heparins are diverse and consist of inhibition of the activation of coagulation, impairment of tumor cell adhesion, inhibition of angiogenesis, inhibition of tumor cell heparinase activity, induction of apoptosis and immune system modulation.[30]

Therapy

Based on available data, derived from clinical trials performed throughout the years, certain recommendations on the application of heparins in oncological patients can be made.

Primary prophylaxis

Hospitalized medical oncological patients are at a high risk of developing VTE, prophylaxis with once daily LMWH of UFH 3 times a day is recommended during hospitalization. The incidence of VTE can be effectively lowered on

prophylactic LMWH treatment in ambulant medical oncological patients undergoing combination therapy with chemotherapeutic agents and for instance thalidomide. Prophylactic low dose VKA is not recommended, because the risk of bleeding equals the risk of VTE without installed anticoagulant therapy. Primary prophylaxis is well established in oncological patients undergoing surgery and prolonged post-hospital therapy with LMWH reduces the incidence of VTE without increasing the risk of major bleeding.

Secondary prophylaxis

The use of LMWH or UFH in treatment of VTE in patients with solid tumors is preferred over VKA. It significantly reduces the risk of recurrent thrombosis without implications for bleeding or mortality rate.

Survival

There is no convincing evidence for an overall beneficial effect of anticoagulant therapy on survival in cancer patients. Certain tumors may be more responsive than others. The median survival improves significantly in patients with small cell lung cancer receiving LMWH in addition to chemotherapy compared to chemotherapy alone. There is a beneficial effect of LMWH in cancer patients with non metastatic solid tumors. The ACCP [31] however does not recommend LMWH for the sole purpose of prolonged survival.

Thrombin generation in patients after acute deep vein thrombosis

Thrombin generation (TG) was assessed in 104 consecutive patients after an acute episode of DVT and compared to a reference range derived from 137 healthy volunteers. Blood was drawn 3 times over the course of 24 months. TG was measured in assays triggered with 1pM of TF and 5 pM of TF; the measurements at 1 pM of TF were performed in the presence and the absence of thrombomodulin (TM).

The first objective of this study was to evaluate whether TG in patients differed form TG in healthy individuals, the second objective was to assess the long term profile of TG in patients after an acute episode of DVT.

Our data show that TG in patients is significantly higher than TG in health individuals, this elevation in TG most likely reflects a hypercoagulable state in these patients. Furthermore, TG varied in time in patients but not in health individuals, suggesting that levels of TG are related to the preceding thrombotic event. Relatively low levels of TG were found one month after cessation of anticoagulant medication.

We furthermore observed that addition of TM lowers TG less efficiently in patients after a recent event of DVT as compared to TG in a reference population. Proteins C and S are determinants of the effect of TM in all patients. Protein C and S were more strongly contributing to the TM effect in patients still on anticoagulant medication. This can be explained by the fact that ETP is lowered by TM in an APC/protein S dependent manner and since treatment with VKA lowers levels of active protein C an S [32], the residual protein C activity is rendered closer to the rate limiting amount of active protein C in these patients. The decrease in ETP following TM is therefore mainly dependent on the amount of residual protein C activity.

Finally, we observed a significant negative correlation between factor (F) VIII levels and TM reduction, after exclusion of patients with FVLeiden mutation from the analysis. This does however not imply that FV is no determinant in TM induced inhibition of TG, but the contributory effect of FV may be too small to be noted at the test conditions used, where F VIII may be a slightly dominant cofactor. The observed negative correlation between f VIII and TM reduction can be explained by enhanced feedback mechanisms through thrombin dependent FVIII activation at increased levels of FVIII, thus counteracting the influence of TM on ETP and PH (acquired APC resistance).FVIII is not dependent on VKA treatment and is already known as a risk factor for recurrent DVT. [33,34] The relation of FVIII with a reduced TM effect on ETP may explain some of the prothrombotic influence of elevated f VIII concentrations in relation to recurrent DVT.

High levels of thrombin generation in relation to increased risk of recurrent thrombosis

We assessed TG in blood (drawn at different points in time) from 125 patients after an acute event of DVT. TG was determined under two experimental conditions: 1 pM TF and 4 μM phospholipids in the absence and presence of 2 nM soluble TM. Blood was obtained from 108 patients; 7 (5.6%) had an objectively documented recurrent event.

The objective of our study was to study the possible relation between recurrent thrombosis and levels of TG, at different points in time, with and without the addition of TM between patients with and patients without a recurrent event.
The second objective of our study was to analyze whether indices of TG were influenced by known risk factors for VTE.

We found that when samples before the recurrent event (PREC) are compared to samples one month after cessation of anticoagulant therapy (B1) or to samples one year after the event (B2) between patients with and patients without recurrent VTE, both ETP (212% (193.5-259) versus 148% (54-187) and 171% (121.6-171.0)) and PH (358 % (310-464) versus 222% (100-303) and 262.4% (144.5-323)) were significantly different.
Upon addition of TM a significant difference in inhibition was seen between samples taken shortly before the recurrence and those taken one month after cessation of anticoagulant therapy (PREC=-9.0% (-14-5.5) - B1= -19.5% (-24.5—17.5)).
Significant associations were found between risk factors for VTE and TG. The LT was associated with: residual thrombosis, previous thrombosis and age. ETP and PH were associated with FVLeiden and gender. Upon addition of TM however, none of the associations remained significant.
In relation to the first objective of our study, we concluded that although we only had a recurrence rate of 5.6%, significant differences could be found for indices of TG between patients with and patients without recurrent thrombosis.
In relation to the second objective of our study we concluded that indices of TG

are significantly associated with known risk factors for VTE, but that in the presence of TM these associations are no longer present.

Individually tailored duration of elastic compression therapy in relation to incidence of the Post Thrombotic Syndrome in patients following an acute event of DVT

We studied the consequence of individually tailored elastic compression therapy in 125 patients after an acute event of DVT. Patients were assessed 5 times during the follow- up period of two years. Patients were managed based on clinical signs and symptoms, as well as results on duplex ultrasound analysis.

The main objective of this study was to assess whether individually adapted duration of elastic compression therapy after initial 6 months of therapy based on a clinical score and results on duplex doppler analysis would influence the incidence of the Post Thrombotic Syndrome (PTS).
A second question was whether or not risk indicators for PTS could be identified.

We found that individualized duration of compression therapy (after an initial 6 months of therapy) results in a two-year cumulative incidence of PTS of 22.4%. This compares well with results of active randomized studies. Hence, it seems that tailoring of the use of elastic stockings, based on a clinical score and results on duplex ultrasound, has no negative impact on the incidence of PTS.
We found that short duration of anticoagulant therapy had a negative association with PTS; OR 0.1(0.02-0.8), reflux on duplex Doppler analysis had a positive association with PTS; OR 7.9 (1.3-48.8), but only when deep as well as superficial reflux were considered. Deep reflux alone was not significantly associated. The most consistent association however was found between PTS and varicositas/venous insufficiency; OR 7.1 (2.3-22.1). This association alone remained significant after correction for other possible risk factors at multivariate logistic regression analysis.
Therefore we may conclude that individualized duration of elastic compression after the initial 6 months of compression may not be inferior to generalized

compression therapy for a period of 24 months. Furthermore, we concluded that extra caution should be taken with patients suffering from varicositas/ venous insufficiency.

PRACTICAL IMPLICATIONS

We have performed a national management study (AMUSE) to evaluate a new diagnostic procedure in the primary care situation. This new diagnostic approach (AMUSE strategy) proved not only to be safe and efficient but also highly feasible. Additional studies to ensure cost-effectiveness as well as optimal performance did have positive outcomes as well. The findings of these studies have resulted in an implementation of the AMUSE strategy in the Dutch general practitioners guideline "NHG standaard".

The studies on the clinical applicability of TG have not yet resulted in implementation of this test in clinical practice, but these studies have added to the conviction that TG has the potential to become a clinical useful test for the global assessment of coagulation.

With the study on the individualization of elastic compression therapy we have shown that although a treatment period of two years for the prevention of PTS is recommended for patients following an acute event of DVT, this may not be necessary for all patients.

RECOMMANDATIONS FOR FUTURE RESEARCH

Diagnosis of DVT

Although great progress has been made by rendering diagnostic procedures for DVT more accessible, simpler and less invasive, still 50% of patients have to undergo a complete diagnostic work-up including referral and imaging. Only 20-25% of these patients will have the disease. Future studies should be aimed at improving identification of patients at high risk.

Health Care Economics

Future (multi-centre) clinical trials should preferably be accompanied by cost effectiveness evaluations. Due to the abundance of available diagnostic

strategies and therapeutic options health care policy makers more and more base decisions on the grounds of disease burden as well as on cost-effectiveness [35]; some countries in Europe even have introduced economic evidence as a formal requirement for decisions regarding resource allocation. The National Institute for Health and Clinical Excellence (NICE) in the U.K. uses economic evidence to support decisions on allocation of publicly funded programmes involving health care. [36] Caution however should be taken not to let future research be restricted by economic requirements and guidelines.

Treatment

Current recommendations for the duration of treatment of venous thromboembolism consider the presence of (transient) risk factors, the extension of the thrombus, concomitant cancer, presence of prothrombotic disorders and the number of previous events. Ideally future therapy recommendations should consider the individual risk profile, including bleeding risk, as well as characteristics of the thrombotic/fibrinolytic balance in individual patients.

In concordance with clinical risk stratification it may be important to further develop a global coagulation assay that reflects the unbalance leading to hypercoagulability. TG has the potential to fit this requirement. Future research should be aimed at the further development and clinical reproducibility of this test ,at unraveling the mechanism of impaired TM inhibition and possibly relate levels of endogenous TG during anticoagulant treatment to the risk of recurrent events. The drawback of most current risk predictors is that they can only be established while off anticoagulant medication.

Future studies on the prevention of PTS should be aimed at individualization of therapy and early identification of patients at risk of PTS. For patients with severe PTS more research has to done towards exploring the therapeutic options such as surgical intervention or thrombolysis.

For specific groups such as cancer patients future research should consider large cohorts of these patients that are sufficiently characterized. New as well as current anticoagulant drugs need to be tested, for anti thrombotic properties, anti

tumor properties, and effects on survival. Both additional clinical trials as well as fundamental biological studies have to be performed.

For new antithrombotic drugs new clinical approaches have to be considered in particular concerning the compliance of treatment. Especially patients on long term treatment may benefit more from the current situation with VKA therapy in which regular checks at the Thrombosis Services are provided.

Evidence in medicine

All practicing clinicians should be aware of the basic requirements of reviewing the literature in order to reach informed conclusions and to be able to put these conclusions in the current clinical perspective.

CONCLUSIONS

This thesis shows that reviewing the literature fulfills an important purpose in the gathering of knowledge and for informed clinical decision making.

Diagnosis as well as treatment of DVT is at the current moment considered to be safe and effective. However, room for improvement can be found in the introduction of diagnostic strategies that are able to better discriminate between patients at high risk and patients at low risk for DVT. The duration of anticoagulant treatment as well the duration of elastic compression therapy should preferably be individually tailored.

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Samenvatting

EVIDENCE BASED MEDICINE

In **hoofdstuk 2** wordt een overzicht gegeven van de criteria waar een systematische literatuurstudie (systematic review) aan moet voldoen. Sinds de negentiger jaren is er een toenemende toepassing van resultaten van op klinisch en translationeel onderzoek berustende bewijslast in de gezondheidszorg en besluitvorming: een concept dat "evidence based medicine" genoemd wordt. (Sacket 1996) Omdat er op grote schaal onderzoek wordt gedaan, en dientengevolge "evidence"wordt gegenereerd op het gebied van trombose, zijn literatuurstudies (reviews) die de uitkomsten van deze onderzoeken samenvatten onmisbaar geworden voor het verwerken van deze groeiende hoeveelheid bewijslast. Het gebruik van deze "samengestelde" kennis is een essentieel onderdeel geworden van de moderne gezondheidszorg. Hierdoor is de patiëntenzorg meer up to date , dynamischer en minder afhankelijk van de persoonlijke ervaring van individuele artsen geworden. Tegelijkertijd kan "evidence based medicine" artsen stimuleren om betrokken te raken bij onderzoek dat kan bijdragen aan verbetering van de patiëntenzorg. Naast het gebruik van literatuurstudies als basis van richtlijnen en besluitvorming ("systematic reviews") kunnen deze studies ook worden gebruikt om een overzicht te geven van ontwikkelingen in een bepaald vakgebied of om bijvoorbeeld de biologische basis van een ziekte beter te begrijpen; de vraagstelling van een systematische review is voor deze toepassing vaak te smal waardoor in deze gevallen de voorkeur uitgaat naar een meer "verhalende" literatuurstudie ("narrative review").

VENEUZE TROMBOEMBOLIE

Veneuze Trombo Embolie (VTE) is een multifactoriële ziekte. Meerdere verworven en genetische factoren, gewoonlijk "risico factoren" genoemd, zijn betrokken bij het ontstaan van trombose. Trombose komt voor bij 2-3 per 1000 personen per jaar en is daarmee een algemeen voorkomende aandoening. Door de vaak aspecifieke klinische presentatie is de klinische diagnose lastig. De diagnose kan alleen met zekerheid worden gesteld op basis van objectieve diagnostische methoden. Slechts een deel van de patiënten met een verdenking op trombose blijkt de aandoening ook daadwerkelijk te hebben. Venografie en

pulmonale angiografie zijn de gouden standard onderzoeken voor de diagnose van respectievelijk diep veneuze trombose (DVT) en long (pulmonaal) embolie (PE). Beide diagnostische methoden worden nog maar zelden gebruikt vanwege de invasiviteit van deze onderzoeken.
Seriële echografie is een veilige diagnostische methode voor de diagnostiek van DVT bij symptomatische patiënten. CT scan is gedocumenteerd veilig voor de diagnostiek van PE. Daar VTE een potentieel levensbedreigende aandoening is, wordt een patiënt met symptomen van trombose doorgestuurd voor objectieve diagnostiek naar speciale diagnostische centra of naar het ziekenhuis. Alhoewel de objectieve testen voor DVT bewezen veilig zijn, heeft de verbeterde bereikbaarheid van niet-invasieve diagnostische testen samen met een verminderde tolerantie voor onzekerheid bij artsen over een periode van 20 jaar tot een verlaging van het percentage positieve echo's geleid van 35% naar 20%. Hierdoor is de benadering waarbij alle patiënten met een verdenking op trombose worden ingestuurd voor objectieve diagnostiek zowel inefficient als kostbaar.

DIAGNOSTISCHE STRATEGIEËN IN DE TWEEDELIJNSGEZONDHEIDSZORG (ZIEKENHUIS)

In de laatste twee decennia, werd er in de tweedelijn gezondheidszorg meer en meer selectief omgegaan met aanvullend objectief diagnostisch onderzoek. Patiënten werden in eerste instantie geselecteerd op basis van een klinische score. Een hoge klinische score gaf daarbij een hoge kans op trombose aan. Evaluatie van klinische waarschijnlijkheidsscores maakte echter duidelijk dat klinische waarschijnlijkheid alleen niet voldoende is om veneuze trombose veilig uit te sluiten. Een combinatie van een D-dimeer assay en klinische waarschijnlijkheid als eerste stap van een diagnostische strategie werd geïntroduceerd door Wells et al. D-dimeer is een fibrine specifiek degradatie produkt en wordt gebruikt als marker voor endogene fibrinolyse in D-dimeer assays. Sindsdien zijn er meerdere studies gedaan in de tweedelijn gezondheidszorg ,waarbij management van patiënten met verdenking op veneuze trombose werd uitgevoerd op basis van een klinische waarschijnlijkheid in combinatie met een D-dimeer assay resultaat. In

hoofdstuk 3 van dit proefschrift wordt een systematische review beschreven over enerzijds de veiligheid van het onthouden van antistollingsbehandeling bij patiënten met een verdenking op DVT gebaseerd op een diagnostische strategie die een klinische score combineert met het resultaat van een D-dimeer assay. Anderzijds wordt de efficiëntie in termen van reductie van het aantal echografische onderzoeken onderzocht. Alle patiënten met een verdenking op veneuze trombose moesten echter voor deze screening naar het ziekenhuis worden ingestuurd. Het is veel gemakkelijker en efficiënter als de selectie zou kunnen worden uitgevoerd bij de eerste presentatie in de huisartsenpraktijk. We concludeerden dat selectie van patiënten op basis van een klinische waarschijnlijkheid en een D-dimeer assay niet alleen veilig is maar ook het aantal uit te voeren echo's kan reduceren.

DIAGNOSTISCHE STRATEGIEËN IN DE EERSTELIJNSGEZONDHEIDSZORG (HUISARTSENPRAKTIJK)

Voordat de diagnostische strategie (gebaseerd op een klinische score en een D-dimeer test) die in het domein van de tweedelijnsgezondheidszorg veilig en efficiënt bevonden was, kon worden geïntroduceerd in de eerstelijnsgezondheidszorg, was validatie in het domein van de eerstelijns gezondheidszorg noodzakelijk. In een validatie studie werd de Wells regel gebruikt in de huisartspraktijk in combinatie met een D-dimeer bepaling in het laboratorium. De accuratesse van de Wells regel in combinatie met een D-dimeer assay was 21% (39% in de tweedelijnsgezondheidszorg) en het percentage van gemiste gevallen van trombose was 2.9% (0.9% in de tweedelijnsgezondheidszorg). De Wells regel werd derhalve niet veilig en efficient genoeg bevonden voor gebruik in de eerstelijns gezondheidszorg. Data verkregen tijdens dit onderzoek werden gebruikt voor multivariate regressie analyse waarbij werd onderzocht tot op welke hoogte combinaties van items die bijdragen aan de diagnose DVT kunnen discrimineren tussen de aanwezigheid en afwezigheid van DVT. Er werd een nieuwe beslisregel gecreëerd (en later gevalideerd), die speciaal ontworpen was voor gebruik in de eerstelijn gezondheidszorg. De recente introductie van point-of-care D-dimeer testen gecombineerd met deze specifieke eerstelijns regel (AMUSE strategie) maakte

het mogelijk een diagnostische strategie geheel in de eerstelijn te laten plaatsvinden. In **hoofdstuk 4** wordt de "AMUSE studie" (Amsterdam Maastricht Utrecht Study on the diagnosis of thromboEmbolism) beschreven, een mangement studie uitgevoerd in de eerstelijnsgezondheidszorg. In dit onderzoek werd de veiligheid en uitvoerbaarheid van selectie van patiënten voor aanvullend echografisch onderzoek op basis van een klinische beslisregel inclusief een "point-of-care" D-dimeer test bij eerste presentatie in de huisartsenpraktijk onderzocht (de AMUSE strategie). Patiënten met een score ≤3 werden niet ingestuurd voor verdere diagnostiek en kregen geen antistolling. Patiënten met een score ≥4 werden ingestuurd voor beeldvormende diagnostiek. Er werden 1002 patiënten geïncludeerd in het onderzoek, 500 (50%) van deze patiënten hoefden geen aanvullende diagnostiek te ondergaan, van deze patiënten ontwikkelden 7 (1.4%;95% CI 0.6-2.9%) patiënten een VTE binnen de 3 maanden follow-up periode. Van de 502 patiënten met een score ≥4 werd in 125(25%) een DVT gediagnostiseerd. Drie patiënten met een negatieve echo ontwikkelden een VTE binnen de follow-up periode van 3 maanden (1.1%;95% CI 0.3-2.7%). We concludeerden dat de AMUSE strategie niet alleen veilig is gezien het lage risico op VTE onder niet verwezen patiënten, maar tevens efficiënt. Het aantal verwijzingen voor echografische evaluatie kan met 50% worden gereduceerd.

In **hoofdstuk 5** wordt beschreven hoe in aansluiting op de management studie werd onderzocht, op basis van de bij het AMUSE onderzoek verkregen data, of de klinische beslisregel aanpassingen behoefde. Onderzocht werd of de accuratesse van de regel (verbeteren veiligheid door verlagen van het aantal gemiste diagnoses en verbeteren efficiëntie door vergroten van het aandeel patiënten dat niet verwezen hoeft te worden) kon worden vergroot. Uitbreiding van de klinische beslisregel met twee variabelen: "DVT in het verleden"en "langdurig reizen" verhoogden de voorspellende waarde van de regressieformule significant; een vertaling naar een update van de klinische beslisregel gaf hierbij echter geen verbetering van de veiligheid en de efficiëntie van de regel. Bij een gelijkblijvende veiligheid (1.4% gemiste VTE) nam de efficiëntie af (43.5% uitsparing van echografisch onderzoek). We concludeerden dat de AMUSE regel geen aanpassing behoeft.

In **hoofdstuk 6** wordt het onderzoek beschreven waarin werd beoordeeld of de gebruikte AMUSE strategie kosten-effectief was in vergelijking met twee gebruikelijke strategiën waarbij verwijzing naar een ziekenhuis noodzakelijk is. Er werd een Markov model geconstrueerd om de kosten en effecten van de verschillende strategiëen voor een langere tijdsperiode te kunnen vergelijken. Er werd gekozen voor een tijdhorizon van 5 jaar en een cyclusduur van 6 maanden. Ten opzichte van de meest efficiënte ziekenhuis strategie leverde de AMUSE strategie een besparing van 138 euro tegen een gering verlies in Qaly (0.002). De ICER (incrementele kost- effeciviteit ratio) lag op 56.436 euro. We concludeerden dat de AMUSE strategie niet alleen veilig maar ook kosten-effectief is.

In **hoofdstuk 7** beschrijven we de karakteristieken en het klinisch beloop van patienten uit de management studie die *niet* werden gediagnostiseerd met trombose, maar behandeld werden in de context van een alternatieve diagnose. De meest voorkomende alternatieve diagnoses waren: spierscheur/hematoom (18.5%), chronisch veneuze insufficiëntie (14.6%), erysipelas/cellulitis (12.6%) en oppervlakkige tromboflebitis (10.9%). Roodheid (OR 21.3) en zwelling (OR 8.6) waren sterk geassocieerd met erysipelas. Afwezigheid van roodheid (OR 0.6) en zwelling (OR 0.6) evenals leeftijd >70 jaar (OR 0.4) en afwezigheid van trauma (OR0.5) waren negatief geassocieerd met de diagnose spierscheur/hematoom. Pijnlijke palpatie van de vene had een sterke associatie met oppervlakkige tromboflebitis (OR 3.7). Een acuut ontstaan van klachten was negatief geassocieerd met chronisch veneuze insufficiëntie (OR 0.5), leeftijd>70 jaar (OR 2) en actieve maligniteiten (OR 2.4), zowel als inactieve maligniteiten (OR 2.1) zijn positief geassocieerd met chronisch veneuze insufficiëntie. Op basis van onze bevindingen concluderen we dat de alternatieve diagnoses voornamelijk worden gekarakteriseerd op basis van de bevindingen bij klinisch onderzoek maar dat ook risicofactoren voor trombose en resultaten van een D-dimeer test aan de diagnose kunnen bijdragen. Voor iets minder dan 30% van de patiënten met een alternatieve diagnose werd geen specifieke behandeling ingesteld maar een afwachtend beleid gevoerd. Voor patiënten met de diagnose oppervlakkige tromboflebitis is mogelijk een actiever beleid geïndiceerd. Patiënten die gedurende de 3 maanden follow-up een DVT

ontwikkelden hadden relatief frequent oppervlakkige tromboflebitis (33% (3/9), p=0.026).

BEHANDELING

Indien trombose wordt gediagnostiseerd, moet de behandeling met antistolling zonder vertraging worden opgestart, omdat trombose een potentieel dodelijke aandoening is. Preventie van een nieuwe episode van trombose is het belangrijkste doel van antistolling bij een acute trombose.

In **hoofdstuk 8** wordt op basis van een literatuurstudie een overzicht gegeven van de huidige inzichten op het gebied van behandeling met vitamine K antagonisten bij veneuze tromboemboliëen. De huidige behandeling en secundaire profylaxe van veneuze trombose heeft twee belangrijke nadelen. Ten eerste, is er de noodzaak tot strikt monitoren van patienten tijdens behandeling met vitamine K antagonisten zodat het fluctueren van de protrombine tijd (vertaald in "international normalized ratio": INR) tot een minimum kan worden beperkt en effectiviteit van therapie kan worden behouden. Een stabiele INR geeft eveneens minder bloedingsrisico. Ten tweede is er na het staken van de therapie een mogelijkheid van recidief trombose. Eerdere studies hebben aangetoond dat voor de meeste patiënten met een therapie gebaseerd op vitamine K antagonisten een INR tussen de 2.0en 3.0 optimaal is. Voor patiënten met trombose ten gevolge van een tijdelijke risicofactor is het niet nodig langer dan 3 maanden te behandelen, terwijl voor andere patiënten ook een minimale duur van een jaar geïndiceerd kan zijn. Nieuwe ontwikkelingen op het gebied van behandeling zijn gericht op verdere individualisering en optimalisering van de duur van de antistollingsbehandeling en op de introductie van nieuwe middelen die geschikt zijn voor langdurige behandeling en niet gemonitored hoeven te worden.

Hoofdstuk 9 geeft eveneens op basis van een literatuurstudie een overzicht van de meest recente inzichten en onderzoeken op het gebied van behandeling met laag moleculair gewicht heparines (LMWH's) bij kankerpatiënten. Voor patiënten met actieve kanker is het beter therapie met vitamine K antagonisten uit te stellen en gedurende de eerste 3-6 maanden te behandelen met LMWH's.

RISICO INDICATOREN VOOR RECIDIEF TROMBOSE

De optimale duur van behandeling met anticoagulantia blijft een onderwerp van debat omdat het nog niet mogelijk is patiënten met een (extreem) hoog van patiënten met een (extreem) laag risico op recidief trombose te onderscheiden. Diverse strategieën zijn aangewend om het risico op een recidief trombose in te schatten, zoals het meten van resttrombose en het meten van stollingsactiviteit na het staken van de therapie met antistolling met behulp van laboratorium bepalingen zoals D-dimeer of Factor (F) VIII spiegels. Echter, de D-dimeer test is eerder een afspeigeling van fibrinolytische activiteit dan van de stollingsactiviteit , terwijl FVIII spiegels slechts één element van de complexe stollingscascade representeren. Dit geldt ook voor de bepalingen van FXI, FIX en protrombine. Al deze bepalingen kunnen worden gebruikt als risico indicatoren voor veneuze trombose omdat de spiegels van deze eiwitten in het bloed geassocieerd zijn met risico op veneuze trombose, echter dit is een omslachtige en kostbare analyse. Er zijn bovendien nog geen goede aanzijzingen dat aparte factor concentraties werkelijk de kans op recidief trombose voorspellen.

Management van patiënten zou mogelijk verbeterd kunnen worden als er een meer globale stollingstest gebruikt zou kunnen worden die de informatie van verschillende losse stollingstesten integreert. De trombine generatie (TG) test lijkt hiervoor een goede kandidaat. TG is de meting van de concentratie van trombine als een functie van de tijd. De meting wordt voornamelijk verricht in bloedplaatjes-arm plasma. Een benadering van een situatie waarin wel bloedplaatjes aanwezig zouden zijn wordt verkregen door toevoeging van fosfolipiden, terwijl de aanwezigheid van een vaatwand wordt nagebootst door toevoeging van twee vaatwand componenten, weefselfactor (“tissue factor”,TF) en trombomoduline (TM). TG begint na activering door TF met een latente fase (“lagtime”, LT) hierin wordt maar weinig trombine gevormd. Deze fase wordt gevolgd door een plotselinge stijging van trombineformatie weergegeven als een piek (PH) in de curve; dit is het moment waarop stolling (de propagatiefase) plaatsvindt. De stoltijd komt daarom overeen met de LT. De trombine wordt direct na vorming geïnactiveerd door antitrombine. Na de piek in trombine generatie daalt de vorming van trombine snel omdat de afbraak proportioneel

toeneemt met de vorming van trombine. Het oppervlak onder de trombinevormingscurve wordt de endogene trombine potentiaal (ETP) genoemd. Eerder werd reeds een associatie met een verhoogd risico op een eerste episode van trombose gevonden bij patiënten met een verhoogde ETP in de TG. Tevens werd een lage kans op recidief trombose gevonden in patiënten na een acute DVT met een lage ETP. In **hoofdstuk 10** wordt een studie beschreven waarin wij de potentiële bruikbaarheid van TG hebben onderzocht. We hebben met behulp van TG middels "Calibrated Automated Thrombogram (CAT) " 104 patiënten geëvalueerd na een episode van acute DVT en de TG in het plasma vergeleken met die in plasma van gezonde vrijwilligers. Er werden duidelijke verschillen gevonden in TG tussen gezonde vrijwilligers en patiënten. Dit verschil was het duidelijkst waarneembaar bij een TF concentratie van 1pM. TG is niet stabiel in de tijd bij patiënten na een DVT in tegenstelling tot TG bij vrijwilligers en na toevoeging van TM wordt TG minder goed geremd bij patiënten na DVT (21%) dan bij vrijwilligers (42.2%). Bij patiënten tijdens antistolling was de remming door TM sterk verminderd (9.7%). Proteïne C en S toonden een significant negatieve correlatie met ETP bij alle patiënten. Een significant negatieve relatie werd gevonden tussen FVIII spiegels en TM reductie van ETP en piek hoogte (PH). Bij hogere FVIII spiegels is er minder remming mogelijk door TM. Wij concludeerden dat er een duidelijk verschil is in TG tussen gezonde personen en patiënten na DVTen dat dit verschil het best waarneembaar is bij 1pM TF.

In **hoofdstuk 11** wordt beschreven in hoeverre waarden van TG tussen patienten mét en zonder een recidief trombose verschillen. Bloed werd verkregen van 108 patiënten waarvan 7(5.6%) een gedocumenteerde recidief trombose hadden doorgemaakt. Er werden significante verschillen gevonden tussen TG bepaald in de laatste afname voor het recidief (PREC) vergeleken met afnames een maand na het staken van de antistollingsmedicatie (B1) voor ETP (212% vs 148% ;p=0.027) en PH (358% vs 191%;p= 0.017), zowel als met die van 12 maanden na het event (B2) voor ETP (212% vs 171%;p= 0.027) en PH (358% vs 262.4%;p= 0.017). Na toevoegen van TM werd een significant verschil in rembaarheid gevonden tussen patiënten met een recidief (-9.0%) en patiënten zonder een recidief (-19.5%). Tevens werd gekeken naar de

mogelijke invloed van bekende risicofactoren voor trombose op TG. Voor diverse variabelen van TG werden associaties met risicofactoren voor trombose vastgesteld. Resttrombose (OR 4.6 (1.6-12.9), eerdere trombose (OR 4.6 (1.1-19.1)) en leeftijd >70 jaar (OR 3.4 (1.0-11.3)) zijn geassocieerd met LT. FVLeiden (ETP:OR 0.2 (0.04-0.7))/(PH:OR 0.2 (0.04-0.7)) en vrouwelijk geslacht (ETP:OR 0.4 (0.15-0.9))/(PH:OR 0.4 (0.2-0.9)) zijn van invloed op ETP en PH. Na toevoegen van TM worden de variabelen van TG niet langer beïnvloed door bekende risicofactoren. Wij concludeerden dat TG de best praktische bruikbaarheid kan hebben in de aanwezigheid van TM. Toekomstige studies zouden gericht moeten zijn op de vraag of er tijdens antistollingstherapie gebruik gemaakt zou kunnen worden van het verschil in rembaarheid met TM tussen patiënten met een grote kans op recidief en patiënten met een geringe kans op recidief.

POST THROMBOTISCH SYNDROOM

Na het doormaken van een episode van DVT is naast de preventie van recidief trombose, de preventie van het posttrombotisch syndroom (PTS) een belangrijk management aspect. PTS is een chronische aandoening die voorkomt in 20-50% van de patiënten na een doorgemaakte DVT. PTS is daarmee de meest voorkomende complicatie van DVT. Posttrombotische klachten ten gevolge van een acute DVT worden toegeschreven aan veneuze hypertensie veroorzaakt door veneuze obstructie of klepschade. Veneuze hypertensie resulteert in een verminderde kuitspierperfusie, verhoogde weefsel doorlaatbaarheid en klinische symptomen typisch voor PTS. De klinische manifestaties van PTS zijn: pijn, oedeem, huidafwijkingen, veneuze claudicatie en in ernstige gevallen kunnen zelfs veneuze ulceraties optreden. Het syndroom reduceert niet alleen de kwaliteit van leven maar is ook verantwoordelijk voor aanzienlijke medische kosten. De incidentie van PTS is dramatisch afgenomen sinds de introductie van elastische compressie therapie. Het is echter nog steeds onduidelijk of alle patiënten op een zelfde manier profijt hebben van deze therapie en of het mogelijk is om patiënten te selecteren met een lage kans op het ontwikkelen van PTS gebaseerd op objectieve klinische testen of subjectieve klachten. In **hoofdstuk 12** beschrijven we een onderzoek waarin we een geindividualiseerde

benadering van elastische compressietherapie onderzoeken. Bij 125 patiënten die op de polikliniek werden vervolgd na het doormaken van een DVT, werd de duur van elastische compressietherapie gebaseerd op de aanwezigheid van posttrombotische klachten en van afwijkingen bij een duplex onderzoek. Op 4 opeenvolgende poliklinische visites (3,6,12 en 24 maanden) werden klachten gescoord volgens de Prandoni score: een klinische schaal met 5 subjectieve symptomen en 6 objectieve tekenen. De objectieve tekenen zijn: pretibiaal oedeem, induratie, nieuwe veneuze ectasieën, roodheid en pijn bij kuitcompressie. De subjectieve symptomen zijn: pijn, kramp, zwaar gevoel, jeuk en tintelingen. Patienten worden gediagnostiseerd met PTS als ze een score van ≥5 hebben op twee opeenvolgende visites met een tussenpoos van 3 maanden. Patienten met een score van ≤4 in de afwezigheid van reflux bij duplex onderzoek werden geadviseerd de elastische compressietherapie te staken. Patienten met reflux mochten eveneens de elastische compressie staken indien de Prandoni score op twee opeenvolgende visites stabiel ≤4 was. Patienten met een score van ≥5 werden geadviseerd om de compressietherapie te continueren. Het duplex onderzoek werd verricht bij 101 patiënten, waarvan 74 enige vorm van reflux hadden, oppervlakkig of diep (73.3%). Van deze patiënten werd de elastische compressietherapie gestaakt bij 31 (31%) in verband met een stabiele score ≤4 bij twee opeenvolgende visites. Echter ook 9 patiënten met reflux en een score ≥5 staakten de therapie. De cumulatieve incidentie van PTS in ons cohort was 13.2% op 6 maanden, 17.6% op 12 maanden en 22.4% op 24 maanden. Deze incidentie komt overeen met de incidenties die bekend zijn uit eerder gerandomiseerd onderzoek waarbij de compressietherapie 24 maanden bedroeg. Wij hebben tevens onderzocht welke risicofactoren voor PTS konden worden geïdentificeerd binnen onze patiënten populatie. Van de geteste variabelen: spataderen/veneuze insufficiëntie, eerdere trombose, overgewicht (BMI>26), leeftijd boven 70 jaar, duur van antistollingbehandeling, resttrombose, reflux, bekende trombofilie en kanker was alleen de aanwezigheid van spataderen/veneuze insufficientie significant geassocieerd met PTS bij mulivariate regressie analyse (p= 0.035, OR 4.7 (1.1-19.7)). De aanwezigheid van spataderen/veneuze insufficiëntie zou mogelijk bij initiële presentatie al gebruikt kunnen worden voor het onderscheiden van

patienten met een hoog risico op PTS van die met een laag risico hierop. De bevindingen van ons onderzoek laten zien dat het individueel aanpassen van de therapieduur op basis van klinische score en duplexonderzoek geen negatieve impact lijkt te hebben op de incidentie van PTS. We concluderen dat voor de meerderheid van de patiënten elastische compressietherapie voor een periode van 6 maanden voldoende lijkt te zijn en dat er een kleine groep patiënten een predispositie heeft voor het ontwikkelen van PTS ondanks het dragen van elastische compressiekousen.

Curriculum vitae

Arina Janna ten Cate -Hoek was born on February 28th, 1960 in Katwijk aan Zee. She graduated secondary school in 1979 at the Pieter Groen College in Katwijk aan Zee. A Colloquium Doctum was obtained at the Free University Amsterdam for physics and chemistry in 1980. In 1980 she started her medical training at the University of Amsterdam. She met her husband at the laboratory for Thrombosis and Hemostasis (Head: Prof. dr. J. W. ten Cate) of the Wilhelmina Gasthuis in Amsterdam during her scientific training on the subject of *clinical and animal experimental studies with a low molecular weight heparin*. She married Hugo ten Cate and later became a mother of two sons (1985 and 1989). In 1987 she and her family moved to Boston, Massachusetts, USA. She took a course in Clinical Epidemiology at Harvard Extension School and worked as a Research Assistant at the Division of Gerontology of the Beth Israel Hospital and Harvard Medical School on the subject of *natriuretic peptide and chronic heart failure*. After their return to Amsterdam in 1990 she worked as a Clinical Research Associate with MIRAI, Amsterdam and was stationed at Lundbeck bv to supervise clinical studies with antidepressant and anxiolytic drugs. In 1994 she started her clinical rounds and fully qualified as a medical doctor in 1996. She gained some experience as a physician working as temporary replacement in nursing homes. After that she started working at the nursinghome Mariahoeve in den Haag part as a physician at the psycho-geriatric clinic and part as a clinical researcher on a study on *improvement of the influenza vaccination strategy in the elderly.*From 1998-1999 she was in training as a nursinghome physician at the LUMC (Leiden University Medical Center) and Oudshoorn nursinghome in Alphen aan de Rijn.

From 2001-2002 she did research at the laboratory for immune pathology, Sanquin (CLB) Amsterdam (Head: Prof.Dr.C.E.Hack). From 2003 until now she is working as a clinician (thrombosis clinic) at the Maastricht University Medical Centre and at the Thrombosis Service Maastricht. December 2004 she started as a PhD-student at Maastricht University at the division of Epidemiology (Head: Prof.dr.M.H.Prins).

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